Lipid-Based Nanocarrier Platforms for Oral Delivery of Poorly Water-Soluble Drugs: Mechanistic Insights, Solidification Strategies, and Patient-Centric Dosage Form Integration

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Abstract

Poorly water-soluble compounds have emerged as a majority of candidates in pharmaceutical development pipelines and their poor oral bioavailability is one of the most important bottle necks between drug discovery and clinical utility. Lipid-based nanocarrier platforms do not try to overcome gastrointestinal physiology, but rather use it, presenting drug molecules in a solubilized, absorbable form from the time they are dispersed in the gut to the time they enter the bloodstream. This review focuses on the mechanistic, formulation, and translational aspects of these platforms in an integrated way, starting with the physicochemical principles for formulation candidacy and then addressing the Lipid Formulation Classification System (LFCS) of the various types of platforms in the field. These sequential absorption mechanisms, including lipolysis-driven micellar solubilization, intestinal lymphatic transport through chylomicron incorporation and P-glycoprotein inhibition by amphiphilic excipients, are studied with mechanistic specificity. In addition to the engineering strategies involved in transforming liquid lipid dispersions into stable solid dosage forms (via adsorption, spray drying and hot-melt extrusion), the practical formulation science of excipient selection, pseudo-ternary phase optimization and biorelevant in vitro characterization is addressed. Therapeutic evidence for a range of drug classes (oncology, antiviral, cardiovascular, immunosuppressant, phytochemical) demonstrates platform versatility and patient population considerations add physiological complexity that is not included in most formulation-focused reviews. New trends such as supersaturable systems, computational formulation optimization, and additive manufacturing herald a more precise and patient-responsive era of lipid-based oral drug delivery.

Keywords: biopharmaceutics classification system, lipid formulation classification system, nanostructured lipid carriers, oral bioavailability, self-nanoemulsifying drug delivery systems, solidification techniques

1. Introduction

The oral route has obtained the maximum patient acceptance, is simple for patients to self-administer and has an established regulatory pathway that no other route can easily match. However, as the pharmaceutical industry has become more reliant on high-throughput screening and structure-based drug discovery, the drug pipeline has been filled with molecules that are powerful, selective and structurally complex, but not suited to oral delivery [1]. It is estimated that around 40% of marketed drugs and over 70% of compounds in development suffer from poor aqueous solubility, a physical and chemical property that directly impacts the systemic exposure achieved by the drug molecule as it is delivered in traditional solid dosage forms [2]. The clinical implications are by no means innocuous; subtherapeutic plasma levels, inconsistent intra- and inter-individual pharmacokinetics, dose increases to overcome poor absorption and even outright failure in some therapeutic areas. Pharmaceutical reaction to this challenge is varied [3]. While salt formation, reduction of particle size by milling, high pressure homogenization, amorphous solid dispersion, cyclodextrin complexation and mesoporous silica based inclusion systems each have their impact on the solubility problem,

the mechanism by which solubility is addressed is not as well integrated physiologically as the lipid based formulation [4]. Lipid-based drug delivery systems take advantage of the digestive and absorptive processes of the body: the solubilization of dietary fat by bile salts, the assembly pathway of the chylomicron in enterocytes, and the lymphatic transport pathway in the intestine to deliver poorly water-soluble drug molecules from the gastrointestinal lumen to the systemic circulation [5]. This isn't a formulation strategy that is against physiology; it's a formulation strategy through physiology, which is a huge reason why we've seen successful commercial oral products in every therapeutic category from immunosuppression to antiviral to antifungal to cardiovascular pharmacology [6].

The lipid nanocarrier platforms that a formulation scientist can use have become much more sophisticated in the last 20 years. The first oral products to use lipids were simply lipid solutions or crude emulsions in soft gelatin capsules [7]. In the meantime, the field has advanced to include self-nanoemulsifying drug delivery systems able to produce droplets of 20 – 200 nm after mild mixing with gastrointestinal fluids, solid lipid nanoparticles and nanostructured lipid carriers, with controllable composition of their matrix and release profile, and lipid nanocapsules, which combine the structural versatility of polymeric nanoparticles with lipid carrier biocompatibility [8]. With the diversification in type of platforms has gone the realization that the liquid lipid dispersions, despite their effectiveness, are severely limited in terms of manufacturability, physical stability and acceptability by the patients, which has fostered a whole new sub-discipline on the solidification of the liquid lipid systems to tablets, capsules, granules and pellets [9].

This review will explore the mechanistic, formulation science and clinical aspects of the lipid based nanocarrier platforms for oral drug delivery in an integrated way. Starting with the physicochemical and biopharmaceutical underpinning of poor oral bioavailability and the rational basis for selecting a lipid-based approach, it builds the classification framework that structures the field, the absorption mechanisms these carriers exploit, the practical science of formulation design and formulation characterization, the therapeutic evidence accumulated across drug classes, and the patient-population considerations that must inform the translation to clinical practice. The review ends with a discussion of the remaining issues and the most promising future avenues for the field. In every case, the focus is on the mechanistic coherence and not on encyclopaedic coverage on understanding why lipid nanocarriers do what they do, not just documenting they do.

2. Physicochemical and Biopharmaceutical Basis of Poor Oral Bioavailability

The sequence of steps that governs the absorption of a drug molecule from gastrointestinal tract to the systemic circulation includes dissolution in luminal fluids, partitioning from luminal fluids across the mucus layer that covers the epithelium, permeation through the enterocyte membrane, escape from intracellular metabolism and efflux transport, transit to portal circulation, and survival of first pass hepatic extraction [10]. For most drugs, the rate limiting step is dissolution or solubilisation in the aqueous luminal environment and it is on this parameter that the physico-chemical properties of the molecule, most importantly aqueous solubility, lipophilicity (Log P), crystal lattice energy (melting point) and molecular weight, determine whether sufficient quantities of drug in solution are available for absorption across the intestinal epithelium [11]. Amidon and co-workers developed the Biopharmaceutics Classification System, which classifies drugs into four classes based on their solubility and intestinal permeability, and thus conceptually explains which of the physicochemical barriers is the predominant one, which is likely to limit the oral bioavailability of a drug [12]. Class II compounds (high permeability and low solubility) may be the most important class for lipid-based formulation development, as these compounds have permeation capacity of the gut wall, but dissolution in the aqueous fluid in the lumen is inadequate to provide an absorbable dose. Class IV compounds have poor solubility and poor permeability, a more complex challenge because the bioavailability cannot be rescued by increasing the solubility if the membrane is an independent barrier. The Drug Classification System takes into account the relationship of the solubility and dose, adding a useful dimension to the system which considers

whether the solubility is insufficient relative to the dose or the transit-limited dissolution, which will have direct consequences on the nature and extent of formulation intervention [13].

An example of an informative parameter for decisions on lipid based formulation is lipophilicity, measured as log P. Log P values > 2 indicate a significant solubility in lipidic vehicles, and this lipid solubility is not just a thermodynamic convenience, but rather a property which allows incorporation of the drug into lipid vehicles such as lipid droplets, micellar structures, and chylomicrons, each of which transports the drug to the intestine [14]. Molecules with log P>5 show a much greater probability of having significant transport via intestinal lymphatics, because they have a strong affinity for the triglyceride-poor chylomicrons synthesized in enterocytes and exported to the mesenteric lymph. A high melting point is a good proxy for crystal lattice energy: the more energy it takes to break apart a molecule from the crystal and generate the more energy to put it in solution, the lower the dissolution rate and solubility [15]. This is why the disruption of crystallinity (or the inability to crystallize, that is, to keep the drug in a solubilized state within the lipid carrier) is a key mechanism of action of lipid-based formulations in enhancing drug dissolution. In addition to solubility, another bioavailability barrier is the activity of efflux transporters, such as the apical membrane enterocyte-expressed P-glycoprotein, which can be affected by lipid-based formulations via the activity of their excipients [16]. Many of the surfactants, such as d-α-tocopherol polyethylene glycol 1000 succinate (TPGS) and polyoxyl 35 castor oil (Cremophor EL), have shown to inhibit the P-glycoprotein efflux activity at concentrations that can be achieved in lipid formulations, which results in increased net transcellular flux of substrate drugs across the enterocyte. Some lipid excipients also affect the activity of the cytochrome P450 3A4 in enterocytes and decrease the presystemic metabolism of Cyp3A4 substrates. These interactions between lipid excipients and GI transport and metabolic machinery are not only a solubilization mechanism but are an additional bioavailability enhancement beyond what is achievable by purely physical means like particle size reduction [17].

Various strategies to improve the bioavailability of drugs can be applied, such as the use of lipid based nanocarriers, but also amorphous solid dispersions, co-crystals, cyclodextrin complexes and nanosuspensions, and a rational choice between these must be made based on the physicochemical profile of the drug and the mechanism of each method, as outlined in Table 1. The critical screening parameters for lipid formulation candidacy are solubility in representative lipidic vehicles at levels greater than about 50 mg/g, a log P > 2, and lack of chemical instability in the presence of fatty acid derived excipients. These criteria ensure that, when fulfilled, the use of lipid-based nanocarriers provides a mechanistically coherent and commercially validated way to enhance oral bioavailability than other technologies relying on physically metastable properties or chemistry of hydrophilic complexation [18].

Table 1. Comparative Overview of Bioavailability Enhancement Strategies for BCS Class II and IV Drugs [19–21]

Strategy	Primary Mechanism	Optimal Drug Candidate Profile	Key Advantages	Key Limitations	Representative Marketed Products
Lipid-based nanocarriers (SEDDS, SLN, NLC)	Solubilization in lipid phase; GI lipolysis; micellar partitioning; lymphatic transport	Log P > 2; solubility in lipid > 50 mg/g; high permeability; thermolabile acceptable	Physiologically integrated; P-gp inhibition; lymphatic targeting; avoids	Oxidative/hydrolytic instability of liquid forms; high surfactant load; IVIVC complexity	Neoral® (cyclosporine A), Norvir® (ritonavir), Aptivus® (tipranavir)

			crystallinity constraints		
Amorphous solid dispersion (ASD)	Conversion to amorphous state increases apparent solubility; polymer stabilizes supersaturation	Moderate log P (1–4); high melting point; good polymer miscibility	Solid, stable dosage form; scalable by HME or spray drying; dose-proportional	Crystallization risk during storage and dissolution; limited drug loading; humidity sensitivity	Kaletra® (lopinavir/ritonavir HME), Zelboraf® (vemurafenib)
Salt formation	Ionization improves aqueous dissolution rate	Ionizable functional group (pKa 3–10); adequate log P for membrane permeation	Simple manufacturing; well-understood regulatory path	Applicable only to ionizable drugs; salt disproportionation under GI pH changes	Diclofenac sodium, atorvastatin calcium
Co-crystal engineering	Crystal packing modification lowers lattice energy; increases intrinsic solubility	Neutral, non-ionizable; flat or planar molecular structure	Does not alter ionization state; can improve both solubility and permeability	Screening-intensive; may exhibit polymorphism; limited approved products	Entresto® (sacubitril/valsartan), caffeine–theophylline
Cyclodextrin complexation	Hydrophobic cavity inclusion improves aqueous solubility	Moderate log P (1–3.5); molecular diameter 5–8 Å; compatible guest dimensions	High solubilization efficiency; well-characterized toxicology	High excipient mass relative to API; competitive displacement in vivo; dose limitations	Sporanox® (itraconazole HP-β-CD), Vfend IV (voriconazole SBECD)
Nanosuspension (particle size reduction)	Increased surface area enhances dissolution rate (Noyes–Whitney)	High log P acceptable; poorly soluble in all solvents; dose > 100 mg	No chemical modification of drug; applicable to high-dose molecules	Ostwald ripening; aggregation on storage; does not address permeability	Rapamune® (sirolimus), Emend® (aprepitant)

3. Classification of Lipid-Based Nanocarrier Systems and the Lipid Formulation Classification System

The spectrum of possible (and available) compositional types of oral lipid delivery platforms, from simple lipid solutions where digestion is necessary to disperse the loaded lipids to nanoscale particulate carriers that disperse without digestion, is so wide that no single mechanistic description fits the whole class. This framework is provided by Pouton's Lipid Formulation Classification System, which was first proposed in 2000 and since then has been refined to categorize lipid-based formulations based on the nature of the excipients and the need for the formulation to be dispersed in the GI environment [22]. Type I formulations consist only of digestible oils (usually long-chain or medium-chain) and do not include a surfactant or cosolvent. They are exclusively reliant on GI lipolysis and bile salt-stabilized emulsification for dispersion and drug solubilization and, therefore, their efficacy is intimately associated with the fed or fasted state and upper GI secretory function [23]. Type II formulations consist of a mixture of water-insoluble surfactants with low HLB and triglycerides, which form coarse emulsions when diluted in water and have a high amount of lipids for lymphatic drug transport. Type IIIA systems contain water-soluble surfactant in addition to lipid and tend to form fine emulsions or microemulsions with droplet sizes <200nm, while Type IIIB systems are basically those that contain predominantly water soluble surfactant and cosolvents, with a relatively small amount of lipid, and that result in a nearly transparent dispersion that does not significantly depend on GI digestion but that has a reduced capacity for lymphatic drug transport. Type IV systems are the most recently identified systems that are surfactant and cosolvent mixtures with little or no lipid vehicle capacity and are intended for use with moderately lipophilic drugs through micellar solubilization [24].

Considering this classification in the context of general lipid nanocarrier taxonomy allows for highlighting of important relationships between composition and structures. At a broad level, the self-emulsifying drug delivery systems and self-nanoemulsifying systems (Type IIIA and IIIB in LFCS) are isotropic liquid mixtures of oil, surfactant and, in many cases, a hydrophilic cosolvent that spontaneously form oil-in-water emulsions or nanoemulsions when gently mixed with an aqueous medium [25]. The mechanism for self-emulsification is thermodynamic, meaning that the interfacial tension has decreased due to the amphiphilic nature of the surfactant molecules and their orientation at the newly created oil-water interface, and the droplet size is determined by the lipid to surfactant ratio, the HLB number of the surfactant and the rate of diffusion of cosolvent from the oil phase into the aqueous phase. Solid lipid nanoparticles, on the other hand, are made of a solid lipid matrix (long-chain fatty acid ester or waxes) which is surrounded by a surfactant layer, and prepared by hot homogenization, microemulsion cooling, or solvent emulsification-diffusion methods, and constitute a particulate platform with matrix-controlled drug release properties different from the rapid dispersion behavior of SEDDS. The disadvantage of solid lipid nanoparticles was that drug expulsion from the nanoparticles during the storage period occurred due to recrystallization of the drug, so to overcome this problem, nanostructured lipid carriers with a defined proportion of a liquid lipid were developed in order to increase the structural disorder of the lipid crystal lattice and thereby decrease the forces of drug recrystallization and increase the resulting encapsulation efficiency over longer storage periods. Lipid nanocapsules are nanoparticles with a liquid lipid core (e.g., medium-chain triglycerides) and a solid shell of polyethylene glycol-grafted surfactants that have a narrow size distribution and are typically in the range of 20–100 nm, and yield a solvent free preparation process utilizing the phase inversion temperature. The compositional ranges, dispersibility characteristics and representative drug candidates for each LFCS type are shown in Table 2 [26].

The value of the LFCS does not stem from its taxonomic accuracy but from its ability to convert the physicochemical properties of a drug, especially its log P and lipid solubility, to a formulation that has a good chance of being absorbed by a specific mechanism. A drug with log P of 6.5 and high solubility in long-chain triglycerides will be a good candidate for a Type I or Type II system where there will be meaningful contribution by lymphatic transport, while a compound with log P of 2.8 and high solubility in a polysorbate system but low solubility in oil will likely be most effective in a Type IIIB or IV system where its absorption mechanism is primarily transcellular, assisted by enhanced solubilization rather than lymphatic partitioning.

The excipient selection and optimization strategies introduced in Section 5 are best used within the context of the matching of drug properties and type of formulation, which is done on the basis of mechanistic logic and not purely empirical screening [27].

Table 2. Lipid Formulation Classification System (LFCS): Compositional Ranges, Dispersion Behavior, Digestion Dependence, and Representative Drug Candidates [28,29]

LFCS Type	Typical Composition	Lipid Content (% w/w)	Surfactant HLB Range	Dependence on GI Digestion	Dispersion Behavior (Aqueous Dilution)	Particle/Droplet Size Range	Lymphatic Transport Potential	Representative Drug Candidates
Type I	Digestible oils only (LCT, MCT)	100%	None	High (complete)	Coarse emulsion with bile; cloudy dispersion	>300 nm	High (especially LCT with log P > 5 drugs)	Halofantrine, vitamin D3, testosterone undecanoate
Type II	Digestible oil + low HLB surfactant (e.g., Span 20)	40–80%	1–9	Moderate to high	Coarse o/w emulsion; opaque	100–300 nm	Moderate to high	Danazol, atovaquone
Type IIIA	Oil + high HLB surfactant + hydrophilic cosolvent	20–50%	11–15	Low to moderate	Fine emulsion; slightly turbid	50–200 nm	Low to moderate	Cyclosporine A (Neoral®), lopinavir
Type IIIB	Predominantly hydrophilic surfactant and cosolvent; minor oil	<20%	>12	Minimal	Microemulsion or clear micellar dispersion	20–100 nm	Low	Ritonavir (Norvir®), itraconazole
Type IV	Surfactant + cosolvent; no or minimal lipid	<5%	Variable	None	Transparent micellar solution	<50 nm	Very low	Amprenavir (Agenerase®), enzalutamide

LCT: long-chain triglycerides; MCT: medium-chain triglycerides; HLB: hydrophilic-lipophilic balance. Drug examples are representative of published formulations and reflect the composition of marketed or extensively studied experimental products.

4. Mechanistic Pathways of Absorption Enhancement by Lipid Nanocarriers

The mechanisms behind the enhanced oral bioavailability of lipid-based nanocarriers must be understood to explain why these nanocarriers are effective in enhancing the oral bioavailability of the drug they are carrying, from the time of ingestion to the point of systemic absorption. It's not just a dissolution-enhancement story, but rather a series of physicochemical and physiological events that can overlap with the normal digestion process of food and can channel drug absorption into alternative pathways not offered to conventional formulations. Liquid lipid formulations are initially mechanically dispersed upon entry into the gastric environment, due to gastric peristalsis and changes in surfactant behavior as a function of pH [29]. Although the gastric environment plays a relatively minor role in the digestion of complex triglycerides, the upper part of the small intestine will take care of that, gastric lipase does initiate some partial hydrolysis of medium-chain and short-chain triglycerides to produce fatty acids and monoglycerides which will start to change the interfacial chemistry of the lipid droplets. As the formulation is transferred to the duodenum, the entire digestive system is present, bile salts are secreted by the gallbladder and pancreatic lipase-colipase complexes at the oil-water interface induce rapid and extensive hydrolysis of triglycerides. Lipolysis products, fatty acids, monoglycerides and diglycerides, are amphiphilic molecules which spontaneously associate with bile salts, phospholipids and cholesterol to form mixed micelles that are generally 2 to 10 nm in diameter. Hydrophobic drug molecules are kept in a solubilized, absorbable state in the intestinal lumen within these mixed micelles, and also in a lesser extent in vesicular structures and larger colloidal particles [30].

This fate of the drug molecules at the transition from the lipid droplet to mixed micelle is mechanistically important and is one of the most important determinants of the in vivo performance of lipid-based formulations. Efficient partitioning into mixed micelles will cause drug to remain in high concentrations at the mucosal surface, thus providing a favorable concentration gradient for passive transcellular diffusion. However, drugs with very high lipophilicity could also tend to stay in the lipid vehicle (undigested or partially digested oil droplets) rather than partition into the micellar phase, and digestion rates of the lipid vehicle (both medium-chain and long-chain triglycerides) could affect the formation of mixed micelles with lower solubilization capacities for highly lipophilic drugs [31]. A known failure mode for lipid formulations, especially for high dose poorly soluble drugs, is that the lipid vehicle may be fully digested and the micellar solubilisation capacity is no longer sufficient to keep the drug in solution. Supersaturation stabilizers are usually hydrophilic polymers like hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate succinate or polyvinyl pyrrolidone added to the formulation at relatively low concentrations that delay the onset of nucleation and slow the crystal growth rate without affecting the equilibrium solubility; this increases the time that supersaturated drug is maintained in the intestinal lumen and is available for absorption [32].

The intestinal lymphatic transport pathway is a mechanistically unique and clinically relevant pathway, which lipid-based formulations can take advantage of for drugs that possess a high enough lipophilicity to do so as depicted in Figure 1. Fatty acids and monoglycerides from the digestion of triglycerides in the intestinal lumen are absorbed by enterocytes, re-esterified to triglycerides in the Smooth Endoplasmic Reticulum and combined with cholesterol esters, phospholipids and apolipoproteins in the form of chylomicrons, which are large lipoprotein particles about 100-500nm in diameter and are secreted from the basolateral membrane of enterocytes into the lacteals of the intestinal villi and thence into the mesenteric lymph [33]. Very lipophilic drug molecules, which have partitioned into the enterocyte lipid pool, are incorporated into newly formed chylomicrons, and hence enter the lymphatics and finally the systemic venous circulation without ever reaching the portal vein or the liver. This bypass is important clinically because certain drugs with a high first-pass hepatic extraction, for example, some of the antiretroviral compounds and immunosuppressants, can have significantly greater systemic bioavailability when formulated to utilize lymphatic transport than when taken through the portal route. In general, incorporation is best achieved with LFCS formulations with high long-chain triglyceride content (Type I and II), where the log P is >5 and the affinity to lipid phases of LFCS is high, as derived from long-chain fatty acids [34].

A third lipid excipients-mediated mechanism to improve bioavailability is the inhibition of P-glycoprotein. The efflux transporter P-gp is encoded by the MDR1 gene, is highly expressed on the apical membrane of enterocytes and can significantly decrease the net intestinal permeability of the substrate molecules by actively transporting them back into the intestinal lumen in an ATP-dependent manner. Excipients such as TPGS, Cremophor EL, Cremophor RH40, and poloxamer 407 are inhibitors of P-gp ATPase activity and membrane fluidity which have been shown to increase trans-cellular permeation and the oral bioavailability of P-gp substrate drugs in cell based and in vivo models in a concentration-dependent manner. This dual mechanism of action (solubilization enhancement and P-gp efflux inhibition) is one of the reasons why the mechanism of action of lipid-based nanocarriers is unique compared with non-lipid solubility enhancement strategies [35].

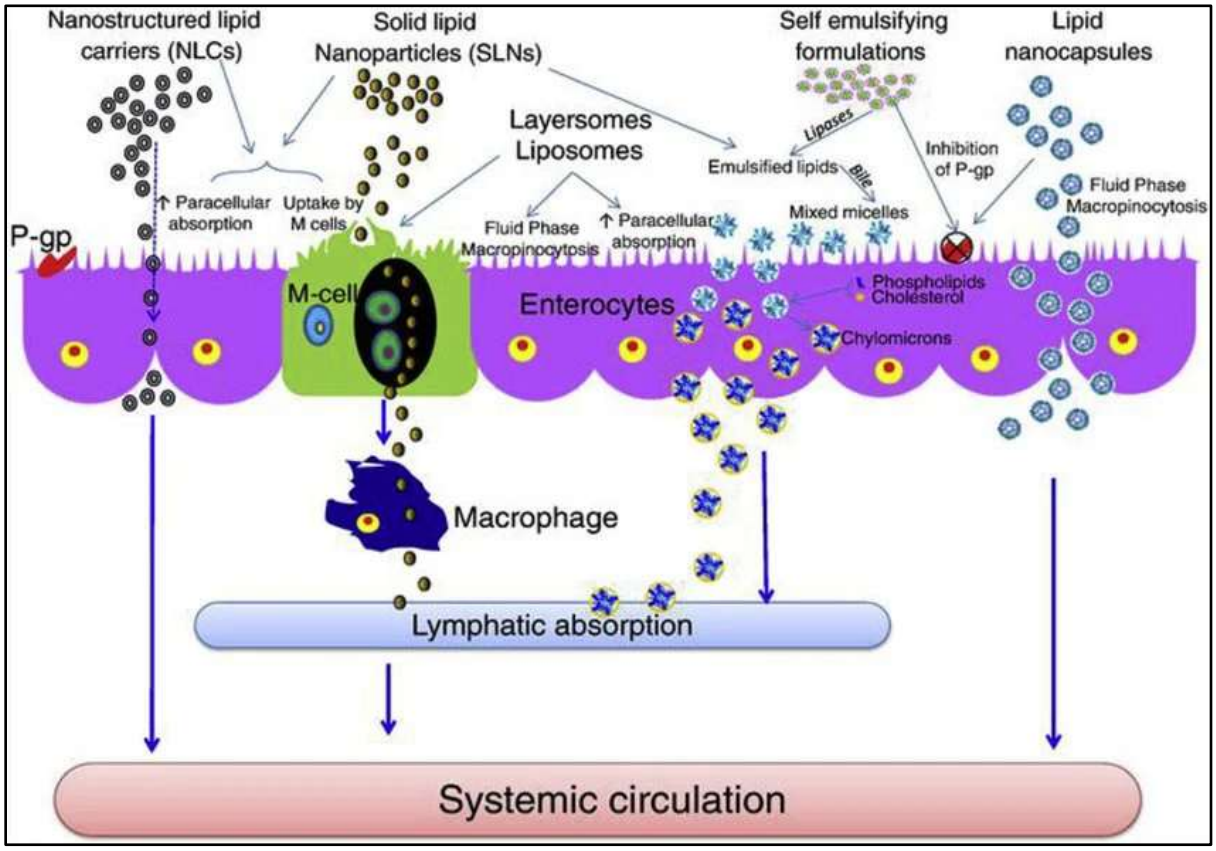

Figure 1: Mechanistic pathways of oral drug absorption from lipid-based nanocarriers in the gastrointestinal tract.

5. Formulation Design Excipient Selection, Optimization, and In Vitro Characterization

The formulation of a lipid-based nanocarrier formulation actually starts with a systematic evaluation of the solubility of the drug in a variety of lipidic excipients, including long-chain triglycerides such as soybean oil, corn oil, medium-chain triglycerides such as Miglyol 812, Captex 300, mixed glycerides such as Maisine 35-1, Capmul MCM, and polyethoxylated castor oils, polysorbates, and glycol-based surfactants, as the practical drug loading capacity of a formulation will be limited by its solubility in the excipient mixture. The initial screen is performed by solubility screening via the shake-flask method or, more efficiently, by miniaturized high-throughput solubility screening where candidates are advanced to pseudo-ternary phase diagram construction to determine the region of self-emulsification as a function of the ratio of oil, surfactant and cosolvent [36]. Beyond solubility capacity, there are trade-offs in terms of the selection of vehicles: long-chain versus medium-chain triglyceride. Long-chain triglycerides yield digestion products that have a greater affinity for chylomicron assembly and thus are the preferred lipid phase when the absorption mechanism is targeted to the lymphatics. Medium-chain variants possess a higher digestibility, a better digestibility, a higher efficiency in the formation of mixed micelles and a lower susceptibility to oxidative rancidity, but a lower micellar solubilization capacity for highly lipophilic drugs and a significantly decreased capacity to afford

lymphatic transport. Thus, the fatty acid chain length of the lipid vehicle acts as a mechanistic lever which the formulation scientist can use to influence the amount of drug absorbed through portal versus lymphatic routes and which can be observed to impact first-pass metabolism and systemic exposure in the appropriate preclinical models [37].

Both thermodynamic and toxicological factors determine surfactant selection. Surfactants with a high HLB polysorbate 80, polyoxyl 40 hydrogenated castor oil, TPGS favor the formation of small oil-in-water droplets, and for this reason are essential for Type IIIA and IIIB systems, but at high concentration are associated with gastrointestinal membrane disruption, unintended increases in mucosal permeability, and hypersensitivity reactions in the case of Cremophor EL at high dose. Interest in using food grade emulsifiers, lecithin-based amphiphiles, and GRAS certified cosolvents has been stimulated by the regulatory requirement to minimize the use of surfactant to the lowest level possible consistent with performance and could be used in conjunction with the synthetic polyethoxylates. The introduction of Labrasol, Labrafil and the related PEG-glyceride excipients has greatly enriched the toolbox with surfactants that have intermediate HLB values and amphiphilic properties, with known tolerability levels in oral formulations [38].

If a formulation composition is found, there are a variety of measurements that are needed to characterize the formulation for regulatory and development needs that goes beyond particle sizing. The primary nanometric quality attribute is droplet size and polydispersity index determined by dynamic light scattering, the surface charge determined as zeta potential and the encapsulation efficiency or drug loading determined by ultracentrifugation or dialysis method. Not less important, and so far underemphasized, is performance characterization under simulated GI conditions, using in vitro lipolysis models. Standardized two stage lipolysis assays, performed with pancreatin enzyme preparations in biorelevant bicarbonate buffered media, at fasted or fed state bile salt and phospholipid content, yields information about the rate and extent of digestion of the triglyceride, the solubilization capacity of the resulting colloidal phase and the percent of drug that precipitates during digestion. These lipolysis model data have demonstrated improved correlation with in vivo absorption when compared to the traditional USP paddle or basket dissolution testing methodology that does not account for the dynamic changes in luminal colloidal composition that help to explain drug solubilization in vivo. This is a well-known problem with lipid-based formulations, and it is a consequence of the poor ability of aqueous dissolution media to mimic the time-varying, complex colloidal environment of the intestinal lumen as lipids are broken down. A more physiologically relevant method for digestion-diffusion models involves the use of a biomimetic barrier material with an in vitro lipolysis compartment and a membrane-based permeation compartment to allow for simultaneous measurement of the solubilization of the drug in the lipolysis compartment and the rate of drug flux in the permeation compartment. However, there is no harmonised method yet endorsed by regulatory bodies for use in bioequivalence or in vitro/ in vivo correlation studies, and the non-standardisation of methods is a bottleneck to their development, which has been an objective for interlaboratory cooperation and method comparison. The decision framework for the choice of formulation type, depending on the drug properties and the translation to in vitro characterization strategy is shown in Figure 2 [39].

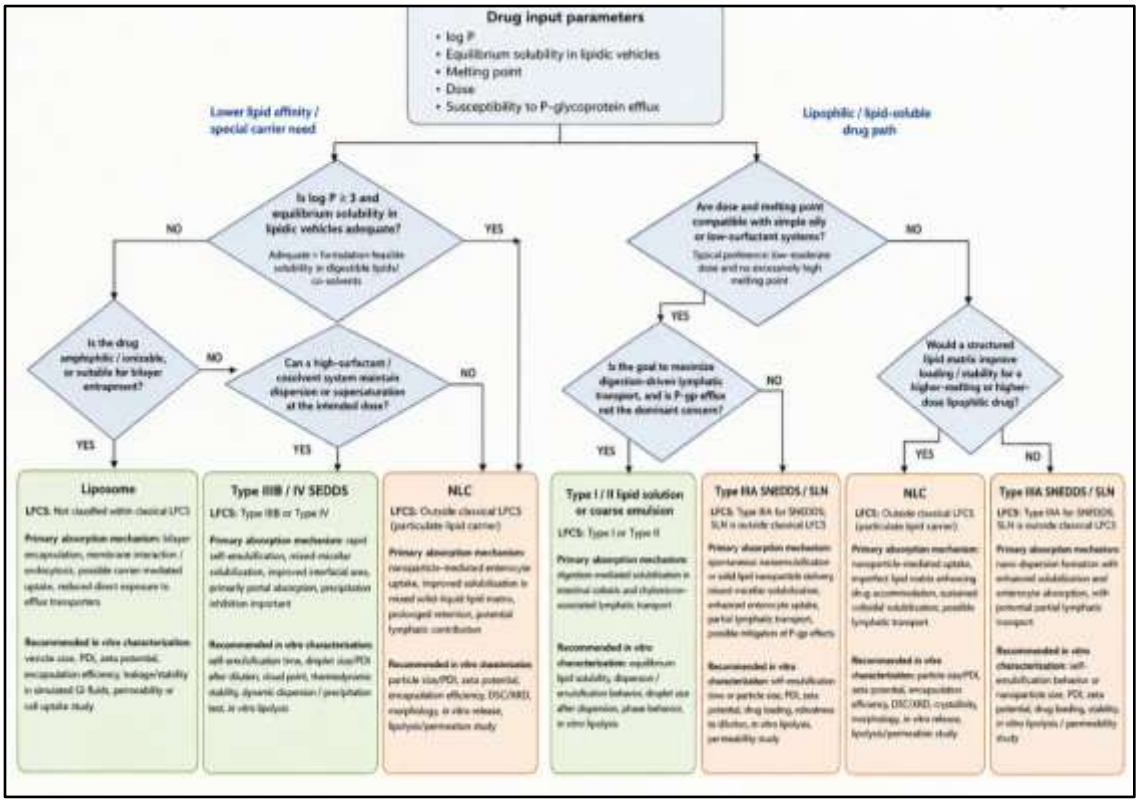

Figure 2: Decision framework for lipid nanocarrier type selection based on drug physicochemical properties and target absorption pathway.

6. Solidification Strategies Engineering the Liquid-to-Solid Transition

Liquid lipid dispersions encapsulated in soft or hard gelatin capsules have been the dosage form of choice for most of the commercial development of lipid-based nanocarrier systems, but it is becoming apparent that this system can present real problems for translation, not just engineering inconveniences. Extensive compatibility testing of capsule shell and lipid excipients is required, the liquid system may be subject to migration, leakage, and interactions with the plasticizers of gelatin capsules; the surface area for oxidative degradation is significant in the liquid system; and product design is limited by lack of manufacturing flexibility tablet compaction, extrusion-spheronization, or granule blending which in turn may limit the amount of drug that can be loaded per unit dose of high-dose compounds. It is scientifically and commercially important, therefore, to convert liquid lipid nanocarrier systems into "solid" powder, granule or tablet intermediate products that maintain the self-emulsifying properties of the original liquid formulation when re-dispersed in GI fluids [40]. Physical adsorption onto solid carriers is one of the simplest solidification techniques suitable especially for laboratory and pilot scale SEDDS and SNEDDS transformation into free-flowing powders. It is thermodynamically simple: porous solid carriers with high specific surface area and large pore volume adsorb the liquid lipid formulation and immobilize the excipient blend in a way that allows it to maintain the oil-surfactant-cosolvent ratio required for self-emulsification when added to aqueous media. In this regard, the most extensively studied inorganic adsorptive carriers include Neusilin US2 (magnesium alumino-metasilicate), Aerosil 200 (fumed silicon dioxide), Syloid XDP 3150 (porous silicon dioxide) and Sylysia 350. Of these, mesoporous silica materials that have pore sizes ranging from 2 to 50 nm and surface areas from 200 to 700 m2/g are the most ideal as they exhibit the best balance of liquid uptake capacity and ability to stabilize the drug, as the confinement of the lipid formulation in nanometre sized pores can be used to prevent drug recrystallization by geometrically restricting drug nucleation, maintain drug-excipient interaction and improve powder flowability over non-porous materials. One of the major pitfalls of solidification by adsorption is the risk of incomplete desorption of the lipid formulation from the carrier pores during GI transit, where the excipient-drug mixture is physically trapped in the pore framework, and does not reform as the intended self-emulsifying formulation, impairing in vivo performance relative to the liquid parent formulation. This failure

mode is not just theoretical, but has been shown by in vitro lipolysis and permeation studies and in vivo pharmacokinetic studies of inorganic carrier based solid SNEDDS compared to the corresponding liquid formulation to be measurably lower in bioavailability, the extent of which is correlated to the pore size and the connectivity of the inorganic carrier [41].

An alternative solidification pathway is spray drying, which can dry the liquid formulation and if a polymeric carrier like Soluplus, HPMC, or PVP-VA is co-dissolved with the lipid formulation, generate composite particles in which the lipid formulation is embedded in or on the surface of a solid polymer matrix. The process is scalable, results in narrow particle size distributions and can be controlled to result in a predominantly amorphous drug state within the solid dispersion—a desired process condition for solubility enhancement, as well as a second mechanism of dissolution enhancement in addition to the self-emulsifying activity of the lipid phase. The main constraint is thermal sensitivity, where high temperatures (typically inlet air temperatures of 100-150 °C) could lead to degradation of the drug or excipients, and it is not easily adaptable to formulations with a high percentage of low viscosity liquid lipids that are not completely encapsulated in the spray-dried droplet. Also hygroscopic formulations can cause significant yield losses at laboratory scale [42].

The third solidification pathway, hot-melt extrusion is mechanistically different from both adsorption and spray drying. During continuous co-extrusion at high shear at high temperature, the drug, lipid components and thermoplastic polymer carrier are extruded together and an amorphous solid dispersion is formed, where the self-emulsifying lipid system is homogeneously dispersed in a polymer matrix. The extrudate, which can be milled and compacted directly into tablets or filled into hard capsules, represents a seamless solidification and final dosage form manufacture process, which is very appealing for industrial scale-up. HME processed compounds can have different solid state characteristics (e.g. increased amorphous drug fraction and decreased crystallinity) from the starting material, with implications for dissolution performance and stability that need to be accounted for in the development process. Spray congealing, melt granulation, and lyophilization are other solidification techniques with limited applications: spray congealing works only for formulations with high-melting lipid components that can be solidified without the use of a polymer carrier, and lyophilization is only applicable when aqueous dispersion stability is a critical factor [43]. These techniques are compared with respect to the parameters most relevant to the formulation development decision-making process in a structured way in Table 3. A parameter of solidification engineering that is not usually explored in sufficient detail is the effect of the conversion process on the self-emulsification efficiency, that is, whether or not the solid intermediate, when dispersed in aqueous media under a gentle agitation that may simulate GI mixing, reconstitute to a droplet size and distribution similar to that of the parent liquid formulation. Self-emulsification efficiency is routinely tested using dispersibility testing in the aqueous medium in which the in vitro release study will be conducted and the droplet size of the reconstituted drug product should be confirmed to meet the droplet size specification that has been set for the liquid formulation. When this equivalence is lost upon solidification (as may happen with surfactant-polymer interactions in spray-dried composites, or with incomplete carrier desorption in adsorbed systems, or with polymer induced changes in the interfacial dynamics of HME extrudates), the most direct sign of the formulation compromise is observed and is also the most telling early warning sign for in vivo performance failure [44].

Table 3. Comparative Summary of Solidification Techniques for Liquid SEDDS/SNEDDS: Carriers, Process Parameters, Impact on Self-Emulsification, and Representative Drug Applications [45]

Solidification Technique	Mechanism of Solidification	Commonly Used Solid Carriers	Key Process Parameters	Self-Emulsification Efficiency	Solid-State Drug Form	Primary Advantages	Key Limitations	Selected Published Drug Examples (2018–2025)

				Preserved				
Physical adsorption onto inorganic mesoporous carriers	Capillary adsorption of liquid SEDDS/SNEDDS into carrier pores; surface immobilization	Neusilin US2, Aerosil 200, Syloid XDP 3150, Sylysia 350, Fujicalin SG	Carrier:liquid SEDDS ratio (typically 1:0.5–1:2); mixing time; temperature	Generally retained if carrier pore volume is sufficient; risk of incomplete desorption with small-pore carriers	Amorphous or microcrystalline (carrier-dependent)	Simple; no thermal exposure; scalable; good flowability	Incomplete desorption; reduced in vivo performance vs. liquid; loading capacity limited by pore volume	Fenofibrate (Neusilin US2), cannabidiol (Fujicalin SG, Neusilin UFL2), rifampicin (Neusilin US2)
Spray drying	Atomization of lipid-polymer solution; rapid solvent evaporation produces composite microparticles	Soluplus, HPMC, PVP-VA 64, Eudragit L100, lactose	Inlet temperature (90–160°C); feed concentration; atomization rate; outlet humidity	Moderate to high; depends on polymer type and surfactant compatibility	Amorphous (polymer-stabilized)	Single-step; scalable; amorphous drug state improves dissolution; narrow PSD	Thermal degradation risk; yield loss; residual solvent; moisture sensitivity of products	Curcumin (Soluplus), celecoxib (calcium silicate + Aerosil), atorvastatin (HPMC E5)
Hot-melt extrusion (HME)	Continuous co-extrusion of drug-lipid-polymer blend at elevated temperature; shear-induced mixing	Kollidon VA64, Soluplus, HPMC-AS, PEG 6000	Barrel temperature (80–180°C); screw design and speed; feed rate; residence time	Variable; dependent on polymer melting behavior and surfactant retention in matrix	Amorphous solid dispersion in polymer matrix	Continuous process; no solvent; directly compressible extrudate; high drug loading feasible	High thermal and shear stress; limited to thermostable drugs; capital-intensive equipment	Ibuprofen (Neusilin US2 + Starch 1500), fenofibraate (Neusilin US2, HME), clozapine (Aerosil + MCC)

Spray congealing	Atomization of melted lipid blend; rapid solidification on cooling	Compritol 888 ATO, Precirol ATO 5, stearic acid, beeswax	Melt temperature; spray nozzle design; inlet air temperature (below lipid melting point)	Moderate; lipid matrix may limit rapid drug release but preserves lipid composition	Semi-crystalline to crystalline lipid matrix	No solvents or polymers needed; good stability for lipid-compatible drugs	Not suitable for Type IIIB/IV systems with low lipid content; limited to meltable lipid formulations	Ibuprofen (Compritol), medroxyprogesterone acetate (glyceryl behenate)
Lyophilization (freeze drying)	Aqueous dispersion of SNEDDS frozen and sublimated; cryoprotectant co-lyophilized	Mannitol, trehalose, sucrose, PVP	Freezing rate; primary drying temperature and duration; cryoprotectant ratio	High if cryoprotectant concentration optimized; reconstitution droplet size critical quality attribute	Amorphous in cryoprotectant matrix	Excellent stability for moisture-sensitive or thermolabile drugs	Batch process; high cost; long cycle time; scale-up complex	Paclitaxel-lipid nanocapsules, amphotericin B-lipid complex (infant SNEDDS)

SEDDS: self-emulsifying drug delivery system; SNEDDS: self-nanoemulsifying drug delivery system; PSD: particle size distribution; HPMC-AS: hydroxypropyl methylcellulose acetate succinate; MCC: microcrystalline cellulose; PEG: polyethylene glycol.

7. Therapeutic Applications Drug Class–Specific Evidence Across BCS Class II and IV Compounds

The translation from formulation science to therapeutic impact is best judged in the context of particular classes of drugs as the meaningful outcome is determined by the drug physichemistry, biological target and required clinical pharmacokinetic properties. The published literature in this field covers a broad spectrum of therapeutic implications, but for the most part, the most mechanistically significant and clinically relevant studies fall into the fields of oncology, antiviral therapy, cardiovascular pharmacology, immunosuppression, and the relatively new area of bioactive phytochemicals, as summarized in Figure 4. Arguably, the most attractive application of lipid nanocarriers for oral delivery is for the delivery of anticancer drugs, which are often BCS Class II or IV drugs with steep pharmacokinetic–pharmacodynamic relationships, and whose conventional formulations require intravenous administration, which makes them difficult to manage clinically. The poor aqueous solubility, P-gp mediated efflux and CYP3A4 intestinal metabolism of paclitaxel, a mitotic spindle poison, have been the subject of extensive studies in lipid nanocarrier formulations [46]. The absolute oral bioavailability of NLC-based oral formulations containing paclitaxel with P-gp inhibitory surfactant was 10–15%, in contrast to approximately 1–3% of conventional oral formulations, and thus reflects

a true mechanistic advance. Oral absorption of docetaxel loaded in SNEDDS with TPGS as surfactant and P-gp inhibitor has also been demonstrated to be significantly improved when compared to suspension of the crystalline drug, in which the AUC was increased by three- to sixfold. A second-generation androgen receptor antagonist, enzalutamide, has also been approved for the treatment of castration-resistant prostate cancer and is available as a soft gelatin capsule containing a lipid-based formulation that provided sufficient oral bioavailability despite enzalutamide's poor aqueous solubility, and the development of solid lipid formulation variants of enzalutamide suggests that the field is maturing around integration into solid dosage forms [47].

The history of drug delivery of antiretrovirals by the oral route is particularly rich, as many HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors are highly lipophilic, P-gp substrates and BCS Class II or IV compounds. The new formulation, a hot-melt extrudate (the Kaletra combination tablet, with lopinavir and ritonavir), showed increased bioavailability, stability at ambient temperature and lower pill burden compared to the original formulation which was liquid and required refrigeration and which was not well tolerated. It is one of the most clinically significant examples of the application of lipid-based formulation science in a real patient population, as the reformulation resulted in a 30% increase in lopinavir AUC, and enhanced compliance and tolerability. In preclinical studies, efavirenz encapsulated in NLC formulations (using Compritol 888 as the solid lipid and oleic acid as the liquid lipid component) has demonstrated bioavailability enhancement in a range of 2.5-fold compared to its commercially available tablet formulation and maintained plasma levels were attributed to the controlled-release properties of the nanostructured lipid matrix. Fenofibrate has a unique and informative place in the cardiovascular drug literature as an instructional example of the effect of the evolution of a formulation aimed at enhancing its bioavailability [48]. The original crystalline fenofibrate tablet formulation had to be taken with food for good absorption; successive generations of reformulation, including the solid SEDDS-based fenofibrate/neusilin tablet formulations reported in academic literature, have led to dose proportionality and elimination of the food effect and to a reduction in dose administered for an equivalent therapeutic effect. In rodent pharmacokinetic studies, bioavailability of the encapsulated Simvastatin and Atorvastatin in SLN and NLC formulations was improved by 1.8- to 2.4-fold, which was attributed to the improved dissolution from the lipid matrix and partial inhibition of first-pass extraction in the liver due to altered kinetics of delivery to the portal vein. These incremental increases in absolute bioavailability of statin drugs that already exhibit moderate to high oral bioavailability in their commercial formulations are significant because they suggest that even for drugs not predicted to benefit from lymphatic transport, the combined dissolution-enhancement and P-gp inhibitory effect of lipid nanocarriers offers some benefit on the pharmacokinetic level [48].

It is noteworthy that the original formulation of cyclosporine A, Sandimmune, a lipid solution formulation was one of the first commercial self-emulsifying drug delivery systems; the pharmacokinetic comparison between Sandimmune and Neoral, in which the latter is a microemulsion-forming lipid formulation, in a clinical population of transplant recipients, established that formulation type within the lipid based category can produce clinically significant differences in drug exposure. The shorter time to peak concentration, smaller inter-patient variability in AUC, and lack of the food effect indicate that the self-emulsifying formulation provides better absorption (both magnitude and predictability) than a conventional lipid solution, with important implications for the therapeutic drug monitoring of Neoral in transplant pharmacology. The study on bioactive phytochemicals with lipid nanocarriers has significantly increased in the past five years (2020-2025), which is boosted by the renewed interest of the pharmaceutical industry in natural products as drug candidates, as well as the realization that many phytochemicals exhibit strong pharmacological activity in vitro but poor in vivo oral bioavailability due to low aqueous solubility, rapid presystemic metabolism, and, in some instances, P-gp efflux. One of the most widely studied curcumin systems are those involving curcumin loaded in NLC formulations, which have been shown to enhance curcumin bioavailability 5- to 9-fold in rodent pharmacokinetic models due to protection from GI degradation, improved micellar solubilization, and/or inhibition of efflux from enterocytes. The bioavailability enhancement of quercetin co-loaded with piperine,

in bioactive SNEDDS, has been reported to be synergistic, which can be attributed to the P-gp inhibitory activity of piperine that increases the absorption promoting effect of the lipid carrier alone. Collectively, the data from these drug class-specific studies, summarized graphically in Figure 4, support the conclusion that lipid nanocarrier platforms do not have a universal positive effect on all poorly soluble drugs, but that they are most likely to be beneficial if the solubility of the drug in a lipidic vehicle is clearly demonstrated, the drug has a log P value that supports micellar partitioning or lymphatic transport, and the absorption barrier features a P-gp or CYP3A4 efflux component [49].

[Figure 4: Graphical summary of in vivo pharmacokinetic enhancement achieved by lipid nanocarrier platforms across selected BCS Class II and IV drug categories. This original figure should present a structured comparative visualization — grouped bar chart or annotated bubble plot — of fold-increase in AUC or relative bioavailability versus the marketed or crystalline drug reference for representative drugs from each therapeutic category (anticancer, antiviral, cardiovascular, immunosuppressant, phytochemical). Each data point should be annotated with the specific nanocarrier type employed and drawn from peer-reviewed publications from 2019 to 2025. The figure should be prepared by the author as an original data synthesis from the cited literature and not reproduced from any previously published visualization.]

8. Patient-Centric Integration Pediatric, Geriatric, and Personalized Dosage Form Considerations

Physicochemical properties of and dissolution behavior in fasted-state dissolution media are not sufficient to predict the performance of a lipid-based nanocarrier formulation in clinical use. There are many differences in gastrointestinal physiology among patient populations, and with direct, often unexpected implications for lipid digestion, micellar solubilization and drug absorption, which the formulation scientist must consider when developing a lipid-based product for pediatric or geriatric use, or for patients with diseases or disorders that affect gastrointestinal (GI) secretory function. Bile salt and pancreatic lipase production is significantly reduced in neonates and young infants compared to adults, and the bile salt pool size is estimated to be ~ 50% of that of adults during the first weeks of life. As the performance of many lipid-based formulations, especially Type I, II and IIIA systems relies on enzymatic lipolysis to produce the mixed micellar species that have the ability to dissolve the drug, this decrease in digestive capacity can result in a lower drug solubilization efficiency and reduced bioavailability than that expected from adult biorelevant dissolution models. A consideration for designing experimental SNEDDS formulations for neonatal drug delivery is therefore that medium-chain triglyceride-based formulations may be more suitable vehicles for drugs than long-chain systems as they do not require as high concentrations of bile salts for efficient digestion and micellar incorporation. In neonates, gastric pH is also raised compared to adults, especially during the first days of life, which further complicates the dosage form design for neonates due to pH dependent behaviour of enteric excipients and ionization/membrane partitioning of weakly acidic drugs [50].

Older persons have an environment in the gastrointestinal tract that is unlike a healthy young adult in several ways: decreased production of gastric acid, delayed gastric emptying, decreased intestinal motility, and age-related alterations in intestinal microflora. Gastric lipase activity and the excretion of bile salts may be reduced in elderly patients with decreased hepatic and gall bladder function, which can affect first-pass digestion of triglyceride rich lipid formulations. In addition, an important concern in the geriatric population is the potential for drug–excipient interactions and for drug–drug interactions with the surfactant components of lipid nanocarrier systems due to co-administration with other drugs with narrow therapeutic windows. These physiological factors indicate that fed-state biorelevant testing, which is not yet well established in the field, should be given more consideration during the formulation process, especially in the elderly-representative GI fluid compositions [51]. Combining solid lipid nanocarrier dispersions with patient-centric dosage form technologies has become a hot topic and considered an active area of solid lipid nanocarrier research to address not only stability and manufacturability but also to incorporate the benefits of swallowability, dose flexibility, and the potential to tailor drug release to the individual patient's pharmacokinetic needs. The lipid-loaded

pellets manufactured by the extrusion-spheronization technique and filled into hard shells as multiparticulate systems provide a lower risk of dose dumping than single-unit tablets, better distribution in the gastrointestinal tract and the opportunity of filling different pellets with different release profiles in the same capsule (which is of relevance for modified-release lipid formulations). The orodispersible mini-tablets containing solidified SNEDDS on mesoporous carriers have been shown to disperse quickly in small amounts of liquid and could therefore be useful for patients who have difficulty swallowing larger-sized tablets, such as young children or elderly persons with dysphagia. Most recently, three-dimensional printing technologies have been evaluated as platforms to prepare patient specific SNEDDS dosage forms with individual drug doses, such as fused deposition modeling (FDM) using thermoplastic capsule shells and extrusion-based direct printing (EBP) using lipid excipients. One practical example showing a clinical feasibility of using FDM-printed capsule shells containing cyclosporine A SNEDDS for precision dosing of a drug with a narrow therapeutic index (NTI) in a patient population where dose individualization is clinically critical was provided by Algahtani and colleagues. The future of formulating poorly water-soluble drugs in lipid-based platforms is therefore foreshadowed by the merging of the science of lipid nanocarriers, the engineering of solidification, and the technology of additive manufacturing [52].

9. Challenges, Regulatory Landscape and Future Perspectives

Although the scientific development and commercial validation of lipid-based nanocarrier platforms are quite advanced, there are still plenty of challenges to overcome for their widespread application and to support decision making in development. Of these, the most practically relevant is the problem of in vitro–in vivo correlations of lipid formulations. Dissolution in compendial media is often predictive of absorption in the fasted human GI tract in solid dosage forms, but for lipid-based systems, this is not the case, as a complex series of digestion, phase changes, and colloidal reorganization occurs in vivo, and this process has not been replicated by any single in vitro model for lipid-based systems sufficiently to enable biowaiver application or to reduce the need for animal pharmacokinetic studies during formulation development [53]. However, the digestion-diffusion models most likely to offer the most promise suffer from a lack of standardization between laboratories and the lack of internationally harmonized in vitro lipolysis testing protocols is a methodological gap that hinders cross-study comparisons and regulatory recognition of model-based development strategies. Although not particularly unfriendly, the regulatory environment for lipid-based nanocarriers lacks specific guidance for this class of nanocarriers. The current expectations for characterisation, stability and safety assessment come from general guidance documents on nanotechnology, ICH guidance documents for quality and existing approved lipid-based products. Uncertainty in the acceptable in vitro characterization methods, definition of critical quality attributes for self-emulsifying systems, acceptability of in vitro lipolysis data instead of in vivo bioavailability studies, and regulatory classification of novel inorganic mesoporous carriers as excipients raise uncertainty that leads to development risk and potentially longer approval times. Specific guidance from FDA, EMA, and ICH on oral lipid-based nanocarrier systems in a harmonized manner would offer the field the platform to translate this vast academic research field into approved products more efficiently [54].

Furthermore, excipient-related safety issues are not addressed as systematically as they should be in literature related to formulation. Many of the high HLB surfactant in Type IIIB and IV systems, such as polyoxyl castor oils, polysorbates, or PEG-grafted glycerides, are known to increase intestinal membrane permeability, inhibit efflux transporters, and affect the absorption of co-administered drugs, which are beneficial for the molecule but may pose risks for pharmacokinetic interaction when administered in combination with other drugs. There is no systematic investigation of chronic exposures to high concentrations of surfactant, for example with twice-daily administration of a maintenance therapy drug, in human subjects and data on long-term GI tolerability with clinical trials specifically designed to evaluate this endpoint are still limited. Future directions of the field can be listed as the following four categories leading to the most productive future [55]. In both in vitro models and in vivo pharmacokinetic studies, Supersaturable SEDDS and SNEDDS (that contain a low

level of precipitation inhibitors like HPMC or HPMC-AS) have proven to be able to achieve a longer period of supersaturation after drug solubilization through lipolysis, and this approach is becoming a well-established formulation strategy with predictive screening tools, representing a near-term opportunity to unlock meaningful improvement in formulation performance for high-dose, poorly soluble drugs where the drug solubility/digestive precipitation is the primary constraint on bioavailability. Rapid progress is being made in the use of machine learning and computational modeling in the development of lipid formulations, including the prediction of drug solubility in lipidic vehicles from molecular descriptors, the computational optimization of oil-surfactant-cosolvent ratio based on Gaussian process regression or artificial neural networks, and physiologically based pharmacokinetic modeling that considers dynamic lipolysis compartments. Lipid nanocarriers that release drug when exposed to pH, enzyme or redox changes in specific regions of the GI tract are a longer-term horizon that could allow site-specific drug delivery, e.g. to the colon for inflammatory bowel disease or to the lymphoid tissue for immunological targets, to a degree not possible with conventional lipid systems. Last but not least, co-delivery of multiple active compounds in a single lipid nanocarrier, which has been shown to work with phytochemical combinations, can be extended to fixed dose combinations of approved drugs that may benefit from co-encapsulation in a shared lipid nanocarrier, due to its bioavailability, drug–drug interaction profile, or therapeutic index [56].

Lipid-based nanocarrier platforms hold a unique place in the field of pharmaceutical formulation. They are not just solubility enhancing technologies in the traditional sense, but physiologically integrated systems that are able to deliver poorly water soluble drug molecules from the gastrointestinal lumen to the systemic circulation in multiple concurrent pathways by engaging the gastrointestinal tract's digestive and absorptive machinery. The mechanisms of lipolysis-driven micellar solubilization, incorporation into chylomicrons and inhibition of P-glycoprotein by amphiphilic excipients are now sufficiently understood to be included in formulation design rather than relying on empirical optimization. Solidification of liquid lipid systems to stable, manufacturable, patient-acceptable solid dosage forms has progressed significantly via adsorption, spray drying, and hot-melt extrusion strategies; however, the mechanistic consequences of each pathway of solidification as regards self-emulsification efficiency and in vivo performance must be understood and controlled explicitly. The therapeutic data in oncology, antiviral pharmacology, cardiovascular medicine, immunosuppression, and phytochemicals-based therapeutics bear witness to the fact that the increase in bioavailability that can be obtained with lipid nanocarriers is clinically relevant for the right drug candidates. The next frontier for the field is the bridge between this formulation science and the physiology of the diverse patient populations, the creation of characterization tools that can be qualified to regulatory standards and provide sufficient assurance of in vivo performance for the reduction of development risk, and the maturation of new technologies, such as supersaturable systems, AI-assisted optimization, and additive manufacturing from proof-of-concept to validated pharmaceutical development tools. Combining these developments, the promise of lipid-based nanocarriers will be realized: not as an "alternative" approach for challenging molecules, but as a first choice for oral delivery of a wide class of clinically relevant therapeutics [57].

10. CONCLUSION

Beyond showing the usefulness of lipid based nanocarriers for delivering individual poorly soluble drugs, the sum of evidence reviewed here suggests that. The mechanistic understanding, formulation science, solidification engineering, and therapeutic pharmacokinetic data that have been gathered over the last 20 years together provide a well-developed scientific framework in which rational decision-making based on drug physicochemistry and absorption biology has gradually taken the place of the empirical screening that was prevalent in early lipid formulation development. These four elements Lipid Formulation Classification System, mechanistic characterization of lymphatic transport and P-glycoprotein inhibition, comparative evaluation of solidification strategies and their microstructural consequences on the self-emulsification efficiency, and drug class–specific pharmacokinetic evidence represent a logical intellectual framework that the pharmaceutical scientist can use with a degree of predictive confidence. The challenges that still need to

be addressed by this architecture are those that are relevant for clinical translation: a lack of validated, regulatory accepted in vitro models that are able to predict in vivo performance with sufficient fidelity to limit the need for animal pharmacokinetic studies; a lack of harmonized guidance on critical quality attributes and acceptable characterization methods specific to solid lipid nanocarrier systems; and insufficient attention to the effect of gastrointestinal physiology differences between paediatric and geriatric populations, as well as disease modified populations, on in vivo performance of formulations optimized in healthy adult biorelevant media. These aren't side lines of technical challenges; these are the problems that stand between a field with a lot of preclinical proof-of-concept and a field with a corresponding number of approved, clinically proven products. The next, most fruitful stage in the evolution of lipid nanocarriers will not be the synthesis of yet another set of nanoparticulate formulations of benchmark drugs, but rather the development and regulatory qualification of predictive in vitro tools, a systematic inclusion of population-specific GI physiology in formulation design, and the use of machine learning to reduce the excipient screening and optimization to a scientifically sound and industrially feasible framework. The space between formulation science and clinical impact will finally close when lipid-based nanocarriers are specifically designed for the patient that will take them, characterized by methods that reflect the GI environment the patient presents and manufactured in solid dosage forms, where performance is guaranteed by mechanistically grounded quality attributes.

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