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REVIEW

Recent approaches to investigate drug delivery systems through the lymphatic pathway using oral lipid-based formulations

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Abstract

Background Lymphatic oral drug delivery systems are considered optimal for enhancing oral drug delivery. They offer the advantage of delivering drugs directly to the immune system while bypassing first-pass metabolism. Consequently, they are actively researched in the field of pharmaceuticals. Novel drug delivery systems are employed to administer drugs through the lymphatic system via the oral route.

Area covered This review delves into the current understanding of drug delivery systems through the lymphatic pathway, with a focus on those utilizing long-chain triglycerides. We explore the mechanisms of delivery to the lymphatic pathway, characteristics of drugs used for this purpose, composition of lipid-based formulations, preparation methods, evaluation methods, and notable case studies.

Expert opinion With the discovery of more lipophilic drug candidates, there is a growing interest in designing formulations to maximize lymphatic transport. Stimulating intestinal lymphatic transport holds the potential for benefits such as reducing first-pass metabolism and delivering high drug concentrations to the lymphatic system. To enhance the utility of intestinal lymph as an alternative means of transport to the systemic circulation, further research is essential. This research should address the underlying mechanisms of drug binding to lipoproteins in intestinal cells, as well as the effects of lipids and formulation excipients on this process.

Keywords Lymphatic pathway · Long-chain triglyceride · Drug delivery system · Lipid-based formulation

Introduction

To optimize the therapeutic efficacy of a drug, it is crucial to carefully choose an administration route that aligns with its unique characteristics and to devise an optimal drug delivery system. While a variety of drug delivery systems have been explored and developed, ongoing efforts continue to create new technologies that align with the unique attributes of newly developed drugs. An examination of LogP values for approved drugs spanning the years 1990–2021 (categorized in 5-year intervals) reveals a consistent increase in both the mean and median drug LogP values over time. The primary factor contributing to this apparent escalation in the overall lipophilicity of drugs is a reduction in the proportion of highly polar molecules. Furthermore, lipids are recognized for their diverse roles in facilitating the absorption of medications from the gastrointestinal tract.

It is well-established that the postprandial absorption of medications is significantly influenced by the consumption of a lipid-rich diet, leading to substantial changes in the bioavailability of formulations. The uptake of drugs by the intestinal lymphatic system presents three potential therapeutic advantages. Firstly, these compounds circumvent first-pass liver metabolism because lymphatic vessels, in contrast to the portal vein, directly drain into the systemic circulation (Shackleford et al. 2003; Trevaskis et al. 2009). Secondly,

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successful targeting of drugs to the lymph, achievable through advanced lipid-based formulations, can enhance the bioavailability of drugs that are otherwise poorly absorbed (Zhang et al. 2016). Thirdly, in certain cases, drug absorption into the lymphatic system augments its therapeutic effects due to significantly elevated lymphatic concentrations. This is observed, for instance, in immunosuppressants and anti-HIV drugs (Takada et al. 1986; Han et al. 2014; Yoshida et al. 2016).

Recent advancements in mRNA technology and lipid nanoparticle-based delivery systems have facilitated the rapid development of mRNA COVID-19 vaccines. This progress has showcased the clinical potential of lipid nanoparticle-mRNA formulations, providing powerful tools for their continued advancement (Hou et al. 2021).

In this review, our objective is to enhance comprehension of lymphatic oral drug delivery systems, with a particular focus on those utilizing long-chain triglycerides. Consequently, we delve into the delivery mechanism to the lymphatic pathway, the characteristics of drugs employed for this purpose, the composition of lipid-based formulations, manufacturing techniques, evaluation methods, and notable case studies.

Lipid-based formulation

Oil solutions, emulsions, dispersions, micelles, self-emulsifying drug delivery systems (SEDDS), and self-microemulsifying drug delivery systems (SMEDDS) can be broadly categorized into four types according to the lipid-based formulation classification system proposed by Pouton (Table 1) (Pouton 2006). Clinical applications for each type are outlined in Table 2. Type I lipid formulations contain oils that require digestion to form mixed micelles. These formulations are typically biocompatible, and they are often the first choice if the active pharmaceutical ingredient (API) dose can be fully solubilized in the vehicle. Examples of drugs formulated as type I lipid formulations include vitamin D analogs and retinoids. Type II lipid formulations consist of a blend of lipids and water-insoluble surfactants (HLB < 12). They self-emulsify into crude oil-in-water emulsions, usually with the application of external energy. Type III lipid formulations include water-soluble surfactants (HLB > 12) and cosolvents. In the presence of an aqueous environment, these formulations spontaneously self-emulsify. Cases where the dispersion droplet size exceeds 200 nm are referred to as SEDDS, while those with a size below 200 nm are termed SMEDDS. In contrast, Type IV lipid formulations are based on water-soluble surfactants and co-solvents, with no inclusion of oil. These formulations enable rapid release and absorption of drugs when in contact with fine dispersions in an aqueous environment. However, this may lead to the

Table 1 Typical composition, characteristic features, advantages, and disadvantages of various lipid-based formulation classification systems

Type	Content of formulation (%, w/w)				Characteristics	Advantages	Disadvantages
	Oils[a]	Water-insoluble surfactants	Water-soluble surfactants	Hydrophilic co-solvents[b]			
Type I	100	–	–	–	Non-dispersing; requires digestion	Generally recognized as safe status; simple; excellent capsule compatibility	Formulation has poor solvent capacity unless drug is highly lipophilic
Type II	40–80	20–60	–	–	SEDDS without water-soluble components	Unlikely to lose solvent capacity on dispersion	Turbid oil in water dispersion (particle size 0.25–2 µm
Type IIIA	40–80	–	20–40	0–40	SEDDS/SMEDDS with water-soluble components	Clear or almost clear dispersion; drug absorption without digestion	Possible loss of solvent capacity on dispersion; less easily digested
Type IIIB	< 20	–	20–50	20–50	SMEDDS with water-soluble components and low oil content	Clear dispersion; drug absorption without digestion	Likely loss of solvent capacity on dispersion
Type IV	–	0–20	30–80	0–50	Oil-free formulation based on surfactants and co-solvents	Good solvents for many drugs; disperses to micellar solution	Loss of solvent capacity on dispersion; may not be digestible

[a]Triglycerides or mixed mono and diglycerides

[b]e.g. Polyethylene glycol, propylene glycol, transcutol

Table 2 Lipid based formulation under clinical trials

Product name	Phase of CT	Drug delivered	Indication
Alocrest (optisomes)	Phase I	Vinorelbine	NSCLC and breast cancers, non-Hodgkin's lymphoma, Hodgkin's disease
ATI-1123 (protein stabilized Liposomes)	Phase I	Docetaxel	NSCLC, gastric, pancreatic cancer, and soft tissue sarcoma
Aroplatin (MLVs)	Phase I/II	Analog of cisplatin	Advanced pancreatic and colorectal cancer, malignant pleural mesothelioma, advanced solid malignancies
SGT-53 (Anti-TfR conjugated cationic liposomes)	Phase I	p53 DNA plasmid	Solid tumors
TKM-080301 (cationic PEGylated Liposomes)	Phase I/II	PLK1 siRNA	Gastrointestinal neuroendocrine tumors, adrenocortical carcinoma, hepatocellular carcinoma
Liposome-annamycin	Phase I/II	annamycin	Breast cancer, acute lymphocytic leukemia
EndoTAG-1 (cationic liposomes)	Phase II	Paclitaxel	Solid tumors
OSI-211 (SUVs)	Phase II	Lurtotecan	NSCLC, breast, colorectal, ovarian, head and neck cancers
CPX-1 (ULVs)	Phase II	Irinotecan and floxuridine (1:1)	Advanced solid tumors, including colorectal cancer
LEP-ETU (anionic liposomes)	Phase II	Paclitaxel	Metastatic breast cancer
Pulmaquin/Lipoquin	Phase II/III	ciprofloxacin	non-cystic fibrosis bronchiectasis
MM-398 (PEP02) (PEGylated liposomes)	Phase III	Irinotecan	Metastatic pancreatic cancer
CPX-351 (bilamellar liposomes)	Phase III	Cytarabine and daunorubicin (5:1)	Acute myeloid leukemia

precipitation of molecules in the gastrointestinal (GI) tract, as these systems are typically limited in their ability to sustain poorly soluble drugs in a solvent.

Excipients for lipid-based formulation

Suppliers provide a variety of lipid excipients, and their impact on the absorption process underscores the importance of comprehending the qualities of different excipients (Pouton and Porter 2008). The selection of excipients for lipid-based formulations is influenced by several factors, including miscibility, solvent capacity, self-dispersibility, and the potential to facilitate the self-dispersion of the formulation. Additionally, considerations encompass digestibility and the fate of the digested products, regulatory concerns (such as irritancy, toxicity, purity, and chemical stability), compatibility with capsules, melting point, and cost.

Lipid-based formulations commonly incorporate dietary oils containing medium- and long-chain triglycerides, along with solvents and surfactants (Christie 1987). These lipids exhibit amphiphilic properties, possessing both lipophilic (fatty acids) and hydrophilic components (Christie 1989). The melting point of these lipids increases with the length of the fatty acid chain but decreases with higher unsaturation, leading to increased susceptibility to oxidation (Jannin et al. 2008).

The Food and Drug Administration (FDA) currently lacks an independent evaluation process or mechanism for assessing the safety of individual excipients. Instead, in the case of premarket-approved drugs or biological products, the excipients undergo evaluation and receive approval as 'components' within the application. From a scientific standpoint, this regulatory approach is reasonable because excipients play a crucial role in the formulation and cannot be evaluated in isolation from the drug. This is particularly pertinent for lipid excipients due to their unique physicochemical properties and their potential for intricate interactions with other ingredients or physiological conditions that may arise in vivo (Chen 2008). The structure of several excipients of lipid-based formulation in Fig. 1.

Triglycerides

Triglyceride vegetable oils serve as predominant excipients in lipid-based drug delivery systems. This specific lipid class raises no safety concerns, as it undergoes complete metabolism and assimilation within the body (Gibson 2007). These vegetable oils are essentially glyceride esters, comprising

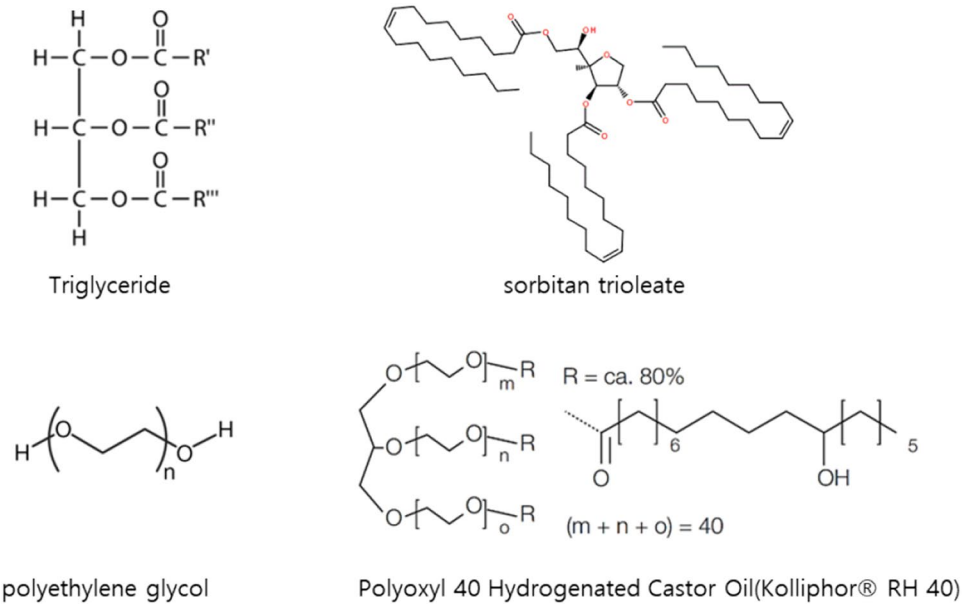

Fig. 1 The structure of several excipients of lipid-based formulation

a blend of unsaturated long-chain fatty acids commonly referred to as long-chain triglycerides. Oils derived from various plant sources exhibit distinct proportions of each fatty acid (Jannin et al. 2008). D-α-tocopheryl polyethylene glycol 1000 succinate (Vitamin E TPGS) is derived from vegetable tocopherols. It is water-soluble and serves as an absorption enhancer for poorly water-soluble drugs. Refined vegetable oils contain pure triglycerides (Collnot et al. 2006, Griffin and O'driscoll 2006; Collnot et al. 2007).

Mixed glycerides and polar oils

Mixed glycerides were produced through the partial hydrolysis of vegetable oils. The composition of these mixed glycerides was determined by the initial material, such as triglycerides, and the extent of hydrolysis. Medium-chain mixed glycerides exhibit resistance to oxidation, possess a high solvent capacity, and contribute to enhanced emulsification. These polar oily additives not only boost the solvent capacity of the formulation but also improve dispersibility (Porter et al. 2004). An illustrative example of such a polar oil is sorbitan trioleate. Oleic acid finds application in various commercial products (Strickley 2007).

Co-solvents

To enhance solubilization, various lipid-based products on the market incorporate water-soluble cosolvents (Porter et al. 2004; Strickley 2007). Commonly utilized materials in lipid-based formulations include polyethylene glycol 400, propylene glycol, ethanol, glycerol, and other cosolvents approved for experimental studies. Cosolvents serve multiple purposes in these formulations. Initially, ethanol was employed in early cyclosporine products to facilitate drug dissolution during manufacturing. Generally, cosolvents are added to boost the solvent capacity of drug formulations that readily dissolve. However, achieving a substantial increase in solvent capacity requires high concentrations of cosolvents, potentially leading to drug precipitation upon mixing with water. Cosolvents rapidly lose their solvent capacity upon dilution (Yalkowsky 1999).

Another function of cosolvents is to disperse systems containing high levels of water-soluble surfactants. Practical constraints on cosolvent concentrations arise due to potential immiscibility with oil components and the risk of incompatibility with capsule shells, particularly with low-molecular-weight cosolvents (Cole et al. 2008).

Water-insoluble surfactants

Non-ionic esters lacking polyethoxylation or polyglycerol modification are categorized as polar oils. In the context of oral lipid-based formulations, we designate a subset of excipients with intermediate Hydrophilic-Lipophilic Balance (HLB) values ranging from 8 to 12 as 'water-insoluble surfactants' (Wakerly et al. 1986). These substances strongly adsorb at oil–water interfaces. Although these materials are not sufficiently hydrophilic to dissolve in water or form micelles, they possess enough hydrophilicity to facilitate self-emulsification (Pouton 1997). The solubility of water-insoluble surfactant components in water is limited, contingent on their degree of ethoxylation, and generally remains quite low. Oleate esters, such as polyoxyethylene

(20) sorbitan trioleate and polyoxyethylene (20) glyceryl trioleate, exemplify water-insoluble surfactants with HLB values ranging from 11 to 11.5. However, the blend of Tween-80 and Polyoxyethylene (80) sorbitan monooleate, with an average HLB value of 11, was not similar to that of polyoxyethylene (20) sorbitan trioleate. The former is composed of both water-soluble and water-insoluble molecules, while the latter is predominantly composed of water-insoluble molecules (Pouton 2000).

Water-soluble surfactants

Surfactants play a crucial role in the development of self-emulsifying drug delivery systems (Pouton 2006). Surfactants with an HLB value of approximately 12 or higher can form micellar solutions even in low water concentrations by surpassing their critical micellar concentration (Hauss 2007). These surfactants can be synthesized by blending polyethylene glycols with hydrolyzed vegetable oils. Alternatively, a common method involves the reaction of alcohols with ethylene oxide to produce alkyl ether ethoxylates, such as the well-known cetostearyl alcohol ethoxylate, also referred to as 'cetomacrogol.' Polysorbates, primarily ether ethoxylates, result from the reaction of sorbitan esters with ethylene oxide (Kolling 2004). Examples such as Cremophor RH40 and RH60, derived from hydrogenated vegetable oils, exemplify this category. Another notable surfactant is Cremophor EL, derived from non-hydrogenated castor oil. Cremophors enhance absorption by inhibiting efflux pumps; however, the specific mechanism of inhibition remains unclear. This phenomenon may arise from non-specific structural changes, where surfactant molecules permeate membranes, adhere to the efflux pump surface, or interact with their intracellular domains (Hugger et al. 2002; Shono et al. 2004; Grove et al. 2007).

Additives

In formulations, it is possible to incorporate lipid-soluble antioxidants, such as α-tocopherol, β-carotene, propyl gallate, butylated hydroxytoluene, or butylated hydroxyanisole. These antioxidants serve the purpose of safeguarding unsaturated fatty acid chains or drugs from oxidation (Gibson 2007).

Long-chain triglycerides oils

Triglycerides are classified based on their chain length as short (up to five carbons), medium (6–12 carbons), or long (more than 12 carbons). Artificial hydrogenation can be applied to reduce unsaturation and enhance resistance to oxidative deterioration. Triglycerides preferentially undergo lymphatic transport or enter the venous system, bypassing first-pass metabolism. The separation of glyceride components in natural product oils is employed to create additives that optimize desirable physical properties and facilitate drug absorption. This process also helps minimize issues such as vulnerability to oxidation (Greenberger et al. 1966). Examples of long-chain triglycerides include corn, olive, peanut, rapeseed, sesame, and soybean oils, which may contain hydrogenated soybean and vegetable oils. Long-chain triglycerides have been utilized in products such as Marino (Dronabinol®) and others (Table 3) (Savla et al. 2017).

Preparation method of lipid-based formulation

Oral delivery is the preferred method for drug administration. Both liquids and solids can be administered through this route. Physically and chemically stable liquids and semi-solids can be converted into solid particles, such as powders or granules. These particles can then be filled into capsules or compressed into tablets using appropriate excipients.

Reverse phase evaporation

The formation of inverted micelles constitutes the fundamental principle underlying reverse-phase evaporation. In this method, lipids were dissolved in an organic solvent, facilitating the generation of inverted micelles. Subsequently, a predetermined quantity of aqueous phase (buffer) was introduced into the solution. The rearrangement of lipids at the water–oil interface resulted in the formation of a water-in-oil (W/O) microemulsion. To achieve a homogeneous dispersion, mechanical or sonication techniques were employed to emulsify W/O microemulsions. The elimination of the organic solvent occurred through continuous rotating evaporation under reduced pressure until a dense gel was obtained. The breakdown of inverted micelles and the subsequent production of lipid vesicles are both favored by slower organic solvent removal (Lombardo and Kiselev 2022). Notably, hepatitis B antigen-loaded solid lipid nanoparticles, modified with a TLR-4 agonist, were prepared using the reverse-phase evaporation method. This approach was chosen to ensure effective colonic uptake of the developed vaccine (Duong et al. 2023).

Spray congealing

The process known as spray cooling involves spraying molten lipids into a cooling chamber, resulting in the formation of solid spherical particles upon contact with cool

Table 3 Commercially marketed product of self-emulsifying drug delivery systems formulations

Drug	Biopharmaceutics classification system class	Trade name/company	Dosage form
Cyclosporin A	IV	Sandimmune®/Novartis	Soft gelatin capsule
–	–	Neoral®/Novartis	Soft gelatin capsule
–	–	Gengraf®/AbbVie	Hard gelatin capsule
Ritonavir	II	Norvir®/AbbVie	Soft gelatin capsule
Saquinavir	IV	Fortovase®/Roche	Soft gelatin capsule
Amprenavir	II	Agenerase®/ClaxoSmithKine	Soft gelatin capsule
Valproic acid	II	Depakene®/ AbbVie	Soft gelatin capsule
Calcitriol	II	Rocaltrol®/Roche	Soft gelatin capsule
Bexarotene	II	Targretin®/Ligand	Soft gelatin capsule
Tretinoin	II	Vesanoid®/Roche	Soft gelatin capsule
Isotretinoin	II	Accutane®/Roche	Soft gelatin capsule
Tipranavir	II	Aptivus®/Boehringer Ingelheim	Soft gelatin capsule
Sirolimus	II	Rapamune®/Pfizer	Oral solution
Efavirenz	II	Sustiva® oral solution/Bristol Meyers Squibb	Hard gelatin capsule
Dronabinol	II	Marinol® /ThePharmaNetwork	Soft gelatin capsule

air. These particles can be administered in the form of capsules or tablets, with ultrasonic atomizers commonly used for this purpose. Rapid solidification depends on key factors such as the excipient melting point, formulation viscosity, and chamber air temperature (Albertini et al. 2008).

In a study conducted by Albertini, Beatrice, et al., various formulations were prepared through spray congealing. A lipid–hydrophilic matrix (e.g., Gelucire® 53/10) served as the carrier, with the addition of several mucoadhesive polymers. This approach led to a significant improvement in the solubility of low-solubility drugs, mucosal adhesion strength, and in vitro bioavailability (Albertini et al. 2009).

Spray drying

The presented method shares similarities with spray congealing, but it diverges in terms of the air temperature within the atomizing chamber. In this approach, the drug solution (comprising the drug dissolved in either an organic solvent or water) is sprayed into a chamber filled with hot air. Subsequently, the organic solvent or water evaporates, resulting in the formation of solid microparticles of the drug. Throughout this procedure, solid carriers, such as silicon dioxide, can be incorporated alongside lipid excipients.

According to Chauhan et al. (2005), the dissolution rate of the poorly water-soluble drug etoricoxib is significantly improved through the preparation of solid dispersions using lipid carriers (e.g., Gelucire™) via a spray drying technique.

Adsorption on solid a carrier

This method is both simple and economical, especially regarding equipment investment. In this approach, a liquid–lipid formulation is absorbed onto a solid carrier, such as silicon dioxide, calcium silicate, or magnesium aluminometasilicate. The liquid–lipid formulation is incorporated into the carrier through blending in a mixer. The choice of the carrier is crucial; it should possess a superior ability to absorb the liquid formulation and exhibit favorable flow properties after absorption. This adsorption technique has proven successful with gentamicin and erythropoietin, utilizing caprylocaproyl polyoxylglyceride formulations. These formulations retained their bioavailability-enhancing effects even after being adsorbed onto carriers (Ito et al. 2005; Venkatesan et al. 2005, 2006).

Melt granulation

The process known as melt granulation involves the transformation of a powder mix, containing a drug, into granules or pellets (Royce et al. 1996; Voinovich et al. 2001; Schaeffer 2004). In this method, a thermosoftening binder is mixed with the drug substance and other excipients under high shear to produce pellets or granules with the desired particle size (Schæfer, Taagegaard et al. 1993; Voinovich et al. 2001; Schaeffer 2004). Depending on the fineness of the powder, 15–25% of a lipid-based binder can be utilized. Key parameters to consider during the process include binder particle size, mixing time, impeller speed, and the viscosity of the binder upon melting (Seo and Schæfer 2001).

Research has shown that the dissolution rate of diazepam can be improved by formulating melt agglomerates containing solid dispersions of diazepam. For example, lactose monohydrate was melt-agglomerated with a meltable binder such as polyethylene glycol 3000 or Gelucire® 50/13 in a high shear mixer (Seo et al. 2003). Melt pelletization has been employed not only to enhance but also to retard the release rate of incorporated drugs (Schæfer and Mathiesen 1996; Thies and Kleinebudde 1999; Voinovich et al. 2000; Mehuys et al. 2004a, b).

Melt extrusion/extrusion spheronization

Extrusion is the process that transforms a raw material with plastic properties into a product of uniform shape and density by compelling it through a die under controlled temperature, product flow, and pressure conditions (Breitenbach 2002, Verreck and Brewster 2004). A "system-in-cylinder" molding technique was employed to create a dual-purpose formulation involving propranolol hydrochloride, aiming to enhance bioavailability and ensure controlled release. The core matrix, composed of a blend of Gelucire® 44/14 and hypromellose, was shaped within an ethylcellulose pipe to safeguard it from hydrodynamic and mechanical stress. Results demonstrated a controlled release of propranolol hydrochloride over 24 h, exhibiting a fourfold increase in oral bioavailability compared to a commercial formulation when tested in dogs (Mehuys et al. 2004a, b; Mehuys et al. 2004a, b; Mehuys et al. 2005).

Supercritical fluid-based method

The presented formulation technique utilizes lipids to coat drug particles, creating solid dispersions. The process involves initially dissolving the drug and lipid-based additives in an organic solvent and subsequently in a supercritical fluid, such as carbon dioxide, achieved through elevating temperature and pressure. Coating is accomplished by controlled reduction in pressure and temperature, causing the solubility of the coating material to decrease and deposit onto drug particles, forming a coating layer (Dos Santos et al. 2003, Thies et al. 2003). Critical considerations for this technique include: (i) solubility of formulation components in the supercritical fluid, (ii) integrity/stability of the active substance under process conditions, and (iii) energy or environmental concerns related to solvent evaporation, if applicable. Various lipid-based and lipid-related additives were explored, including glyceryl trimyristate (e.g., Dynasan™ 114) and stearoyl polyoxylglycerides (e.g., Gelucire® 50/02) for controlled-release applications (Sethia and Squillante 2002; Dos Santos et al. 2003; Thies et al. 2003; Sethia and Squillante 2004).

Recent advancements include the effective enhancement of carbamazepine bioavailability using Vitamin E TPGS and Gelucire® 44/14. Solid dispersions of carbamazepine were prepared employing either the traditional solvent evaporation technique or the supercritical carbon dioxide method. Both methods and additives increased intrinsic dissolution rates of carbamazepine. Although all formulations improved drug bioavailability, the degree of enhancement varied based on the additive and method used. Vitamin E TPGS performed better with the supercritical fluid method, while Gelucire® 44/14 exhibited superior results with the classic solvent evaporation method.

Lymphatic pathway of lipid-based formulation

In lipid-based delivery systems, vehicles undergo transformation into secondary lyotropic vesicular and micellar structures, exhibiting enhanced mucus-penetrating ability upon lipolysis by constituent lipid-acting lipases in the gastrointestinal tract (Zhang et al. 2021). Post-lipolysis in the intestinal lumen, primarily 2-monoglycerides, fatty acids, and monoglycerides are released and subsequently absorbed by enterocytes. This absorption is facilitated through a mechanism mediated by fatty acid-binding membrane proteins and fatty acid-related transporters residing on the apical membrane surfaces (Berthelsen et al. 2019). Chylomicrons (CMs), lipid spheroids formed in enterocytes in response to lipid ingestion and digestion, play a pivotal role in transporting lipids, especially highly lipophilic triglycerides (TG). The common structure of the CM comprises TG and cholesterol esters in the core, surrounded by phospholipids, cholesterol, and wrapping proteins on the surface (Beilstein et al. 2016).

Following a series of intracellular processes, pre-CMs mature into CMs that are secreted into the mesenteric lymph and subsequently transferred via the lymphatics into the systemic circulation (Zhang et al. 2021) The typical intestinal tract is abundantly supplied with both blood and lymph due to the close proximity of the lamina propria surrounding the enterocytes to blood and lymph vessels. After absorption and transition across enterocytes, two potential scenarios may unfold. In one scenario, drugs may prefer entry into blood capillaries, while in the other, entry into lymph capillaries is favored. The former pathway, wherein absorbed drugs are transported into the portal blood, is the most common mechanism due to the higher rate of fluid flow in the portal blood compared to that in the intestinal lymph (500-fold higher for portal blood) (Trevaskis et al. 2008). Large or high molecular weight drugs face limitations in

diffusing across blood capillaries and thus utilize more permeable lymphatic capillaries for absorption. Lipoproteins play a crucial role upon entry into the enterocyte, binding to macromolecules to facilitate the entry process and, more importantly, aiding in movement across the enterocyte. The physical size of lipoproteins varies, restricting their diffusion across vascular endothelium. Consequently, lipoprotein size limitations in diffusion, combined with the unobstructed diffusion across lymphatic capillaries, result in the preferential access of lipoproteins and the drug to the lymphatics (Yáñez et al. 2011).

Drug-related factors for delivery to the lymphatic system

The physicochemical properties of drugs play a critical role in determining the efficacy of oral delivery to the lymphatic system, as they impact the loading or concentration of drugs per chylomicron. These properties, which are summarized in Table 4, include the partition coefficient and TG solubility, with the latter being particularly vital for lymphatic delivery. Charman and Stella (1986) proposed that effective drug candidates should have a LogP > 5 and TG solubility > 50 mg/mL. In their study, they compared the lymphatic transport of dichlorodiphenyltrichloroethane (LogP 6.19) with hexachlorobenzene (LogP 6.53). Despite similar LogP values, 33.5% and 2.3% of the administered dosages of dichlorodiphenyltrichloroethane and hexachlorobenzene, respectively, reached the lymphatic system, primarily due to a 13-fold difference in TG solubility between the two compounds (Charman and Stella 1986; Myers and Stella 1992). However, it is noteworthy that a high partition coefficient and TG solubility is not sufficient for lymphatic drug delivery. For instance, in one trial, only 3% of the administered panclomedine, with a LogP of 5.48 and TG solubility of 175 mg/mL, reached the intestinal lymph. Similarly, CI-976, a lipophilic lipid regulator with a LogP of 5.83 and TG solubility > 100 mg/mL, exhibited very poor transport, with < 1% of the dose reaching the intestinal lymph (Myers and Stella 1992).

We observed weak correlations between intestinal lymphatic bioavailability and logP ($r^2 = 0.50$, P = 0.0326), solubility in long-chain triglycerides ($r^2 = 0.55$, P = 0.0341), and molecular weight ($r^2 = 0.12$, P = 0.3828). Similarly, the correlations between the uptake of lipophilic compounds by the isolated CM and LogP ($r^2 = 0.48$, P = 0.0182), solubility in long-chain triglycerides ($r^2 = 0.55$, P = 0.0147), and molecular weight ($r^2 = 0.12$, P = 0.2974) were found to be weak (Gershkovich and Hoffman 2005).

The logarithm of octanol solubility (log [Oct]) exhibited a linear relationship with the predicted LogP, unrelated to poor water solubility. A Log[Oct] value > 2.5 might serve as a more reliable predictor of suitability in lipid-based drug delivery systems than LogP alone (Savla et al. 2017).

The partition coefficient and solubility in TG are crucial factors influencing the lymphatic transport of a drug. However, further research is required to definitively identify all the key factors contributing to the successful lymphatic transport of drugs (Kim et al. 2013).

Table 4 Summary of physicochemical properties of some drugs

Compound	MW	LogP	Solubility in LCT (mg/g) (mean ± S.D.)
Diazepam	284.7	2.70[a]	15.45 ± 0.41[§§]
Testosterone	288.4	3.27[a]	8.25 ± 0.30[§§]
CSA	1202.6	2.92[b]	44.9 ± 15.1[§]
Halofantrine	500.4	8.5[c]	47.3 ± 6.5[§§]
Vitamin D_3	384.6	9.14[a]	168.3 ± 26.3[§]
Vitamin E	430.7	12.18[a]	Miscible
Probucol	519.9	10.91[a]	60.9 ± 4.7[§§]
Bifonazole	310.4	5.71[a]	3.65 ± 0.07[§§]
Paclitaxel	853.9	4[d]	0.53 ± 0.03[§]
Benzo[*a*]pyrene	252.3	6.11[a]	16.57 ± 1.12[§§]
p,p'-DDT	354.5	6.79[a]	176.57 ± 8.45[§§]

[a]Calculated using the on-line version of LogKow (KowWin)

[b]Calculated value from (El Tayar et al. 1993)

[c]Calculated value from (Caliph et al. 2000)

[d]Experimental value from (Niethammer et al. 2001)

[e]Experimental value from (Kaukonen et al. 2004)

[§]Duplicates

[§§]Triplicates

Models for evaluation of lymphatic transport

Numerous models have been created to evaluate lymphatic transport. In vitro models seek to replicate the digestive processes and functions of either M cells or CMs. In contrast, in vivo models primarily focus on gathering data and estimating drug transport through the lymphatic system via lymphatic cannulation. The digestion model utilized to assess lipid-based drug delivery systems is detailed in Table 5.

In vitro model: in vitro digestion models

When simulating the intricate physiological and physicochemical events occurring in the human GI tract after the oral administration of a lipid-based drug delivery system, it is essential to ensure that each stage of the digestion process closely mirrors realistic pH and enzymatic conditions, transit times, and mixing. Moreover, consideration must be given to factors such as the resident microbiota, immune system,

Table 5 Overview of presently designed digestion-permeation models used to evaluate lipid-based drug delivery systems (Crum et al. 2016; Bibi et al. 2017; Keemink and Bergström 2018; Alskär et al. 2019; Keemink et al. 2019)

Model design	Dahan and Hoffman	Crum et al	Bibi et al	Keemink and Bergström	Keemink et al Alskär et al	Klitgaard et al
Setup for permeation	Ussing chambers	In situ rat perfusion	Ussing chambers	Transwell system	Two compartmental simultaneous setup	Franz diffusion cell
Transfer of lipolysis content	Following 30 min of controlled lipolysis	Continuous transfer by peristaltic pump	Following 10 min of controlled lipolysis	Following 60 min of controlled lipolysis	Simultaneous	Following 0, 15, 30 and 60 min of controlled lipolysis
Permeation barrier	Rat jejunum (ex vivo)	Rat jejunum (in situ)	PermeaPad®	Caco-2 monolayer	Caco-2 monolayer	PermeaPad®
Acceptor medium	Modified Ringer buffer	Mesenteric vein	FaSSIF-V2-Blank buffer	HBSS	HBSS with 4% (w/v) BSA	PBS with 4% (w/v) BSA
IVIVC from lipolysis	Yes	No	Not evaluated	Not evaluated	No	No
IVIVC from combined setup	No	Yes	Not evaluated	Not evaluated	Yes	Yes

BSA Bovine serum albumin, *HBSS* Hank's balanced salt solution, *PBS* Phosphate buffered saline

feedback mechanisms, and specific hormonal controls to accurately replicate human digestion (Guerra et al. 2012). Additionally, to achieve an accurate prediction of the in vivo behavior of lipid-based drug delivery systems, it may be necessary to mimic the uptake mechanism in the small intestine, lymphatic transport, and hepatic metabolism. Unfortunately, the simulation of these complex multistage processes is technically challenging, time-consuming, and costly. Therefore, working under the assumption that a simplified digestion model can effectively capture the relevant effects of human GI digestion on the oral performance of lipid-based drug delivery systems, a series of simplified in vitro digestion models were developed.

The most commonly utilized in vitro digestion models for evaluating lipid-based drug delivery systems focus on simulating enzymatic digestion. These models typically replicate the intestinal (or both gastric and intestinal) phase of digestion using physiologically relevant media designed to mimic GI fluids, including digestive enzymes, at relevant activities. All experiments were conducted at 37 °C, often maintaining a fixed pH. Notably, within the field of food sciences, in vitro models commonly incorporate digestion in the oral cavity (Lucas-González et al. 2018).

While most in vitro digestion models for lipid-based drug delivery systems primarily concentrate on enzymatic digestion processes, there are alternative approaches. Simple dispersion tests, which involve no added enzymes, can be regarded as basic in vitro models that only simulate the preprocessing of lipid-based drug delivery systems during gastric mechanical digestion in vivo. Furthermore, the dynamic gastric model and TNO gastrointestinal model 1, originally designed for food research, prove suitable for studying both enzymatic digestion and the impact of gastric emptying rate and GI hydrodynamics on lipid-based drug delivery systems (Griffin et al. 2014).

In vitro model: chylomicron association model

The virtual association of drug molecules with chylomicrons in enterocytes governs the efficiency of lymphatic drug transport. The in vitro chylomicron association model holds significant promise in providing crucial insights for predicting in vivo mesenteric transport. Dichlorodiphenyltrichloroethane, exhibiting a higher affinity for chylomicrons, demonstrated markedly increased lymphatic transport compared to diazepam, which exhibits limited binding efficiency (Fig. 2) (Gershkovich and Hoffman 2007). A linear correlation between chylomicron-binding capability and lymphatic transport was established using nine fat-soluble components, including halofantrine, probucol, and vitamins, among others (Gershkovich and Hoffman 2005). This correlation was further validated using a physicochemical in silico model.

While natural chylomicrons may offer superior predictive capabilities, biomimetic chylomicrons are preferred due to their lower intergroup variations, reduced sacrifice of animals, and the elimination of labor-intensive procedures involved in natural chylomicron separation (Lu et al. 2015). In addition to the fundamental physicochemical properties of drugs, various factors, such as the addition of surfactants, may play a crucial role in altering drug solubility (Kim et al. 2015). Therefore, the contribution of excipients should also be taken into consideration.

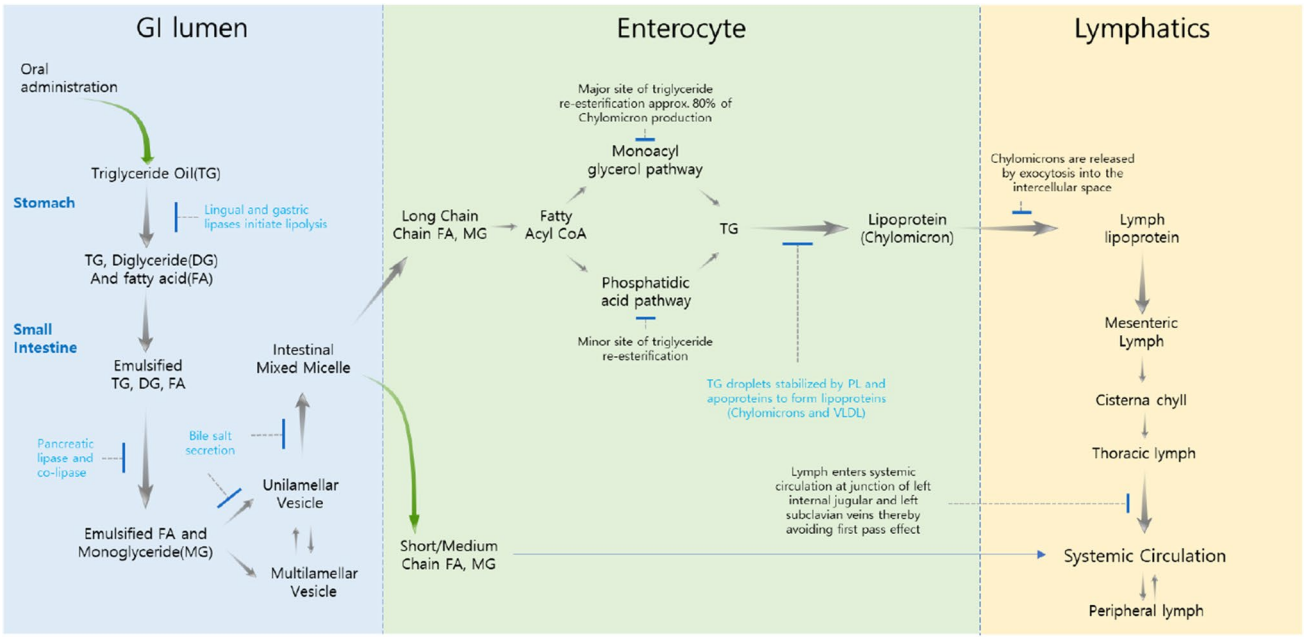

Fig. 2 Oral lipid digestion and lymphatic pathway by utilizing chylomicron

In vitro model: combined digestion-permeation model

Most of the digestion-permeation models designed employ the conventional pH–stat lipolysis model for simulating digestion. In this process, the digested contents are subsequently transferred to a distinct compartment for the permeation step (Table 5).

In vivo model: lymphatic cannulation model

The absorption of particles or drug-associated CMs occurs through lacteals from the apical side coverage at the mesenteric lymphatics. To effectively collect and measure total lymphatic drug transport, mesenteric lymphatic cannulation emerges as a favorable approach. A model employing mesenteric lymphatic cannulation was established and utilized for evaluating lymphatic transport (Holm et al. 2003). Details of the surgical procedures can be found in the literature (Chaudhary et al. 2014).

Large animals such as pigs and dogs are preferred over smaller counterparts like rats and mice due to their physiological and anatomical similarities, especially in aspects like biliary secretion, when compared to humans (Edwards et al. 2001). Nevertheless, rat models remain the most popular. Notwithstanding the simplicity of sample collection and quantification, lymphatic cannulation is an invasive technique with inherent limitations (Trevaskis et al. 2015). The procedure involves intricate surgery and may potentially affect lymph flow and vessel pressure gradients, posing challenges for consecutive sampling after multiple treatments. Due to the influence of various factors, the success rate of lymphatic cannulation is generally low (Patel and Sawant 2019).

In vivo model: lymph blocking model

To alleviate the challenges associated with cannulation-related operational stress, lymph-blocking models have been established using blocking reagents. Cycloheximide, a protein synthesis inhibitor, selectively suppresses CM secretion without affecting other absorption pathways. Despite the irreversible nature of the blockage, no apparent adverse effects have been reported (Dahan and Hoffman 2005). The robust correlation observed between the CM blocking model and the lymphatic cannulation model validates its reliability in predicting lymphatic absorption (Lind et al. 2008). However, the specificity of cycloheximide in blocking CMs remains uncertain. Research suggests that cycloheximide may also inhibit M cells, thereby compromising the accuracy of estimating the CM pathway (Sun et al. 2011).

In vitro–in vivo correlation (IVIVC)

The enhancement of lipid-based formulation development and commercialization potential can be significantly achieved through in vitro-in vivo correlations.

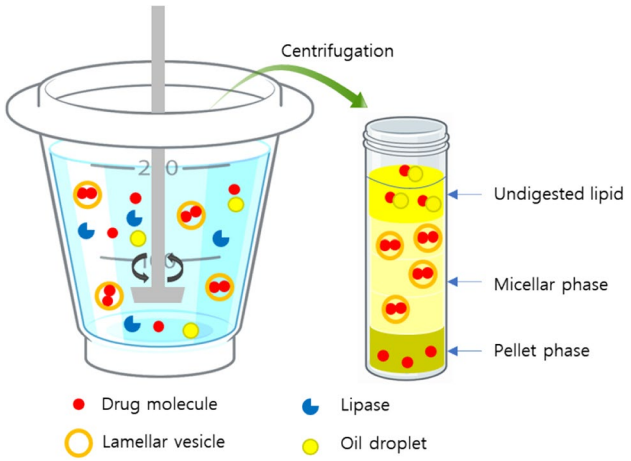

Fig. 3 Schematic representation of the one-compartment lipolysis model

Establishing a model that connects in vitro and in vivo data not only shortens the drug development timeline but also improves product quality. Various in vitro techniques, including assessing solubility, dissolution, and lipolysis of lipid excipients, along with intestinal membrane techniques such as isolated animal tissue and cell culture models, can be employed to evaluate lipid-based formulations (Seeballuck et al. 2003). The pH–stat lipolysis model, which mainly simulates enzymatic digestion, is the most frequently used model in the evaluation of lipid-based formulations (Fig. 3). While these techniques provide insights into specific formulation aspects, it is crucial to recognize their limitations in understanding the in vivo interactions and performance of such systems. Similar to enterocytes, Caco-2 cells produce and release chylomicrons upon exposure to lipids. Additional research is needed to identify the most suitable in vivo model for evaluating lipid-based formulations. Dahan and Hoffman (2007) conducted a study on the effect of different lipid-based formulations of lipophilic drugs on in vitro solubilization and ex vivo intestinal permeability processes. They predicted the in vivo oral bioavailability of two model drugs, griseofulvin and dexamethasone, by designing in vitro lipolysis and ex vivo intestinal permeability models. Both drugs exhibited a good correlation between their in vitro and in vivo data regarding lipolysis and absorption. However, the actual in vivo data did not align with the ex vivo permeation studies. Griseofulvin, with limited solubility (5 µg/mL), is influenced by the presence of lipid excipients, bile salts, phospholipids, and lipolytic products in the digestive media. Therefore, the careful selection of the most appropriate in vitro and in vivo models is paramount for establishing reliable in vitro–in vivo correlations in lipid-based formulations.

Conclusion

This overview summarizes research developments aimed at gaining a better understanding of the unique characteristics of the lymphatic system. Given the effective sale of numerous medications in lipid-based formulations, lipid-based drug delivery systems exhibit a wide range of potential applications for enhancing solubility and bioavailability.

In recent times, there has been a growing interest in understanding the mechanisms through which drugs enter the lymph, the formulation strategies that can either maximize or minimize lymphatic transport, and the potential impacts of lymphatic transport on drug processing within enterocytes and the liver. The potential advantages of stimulating intestinal lymphatic transport include a reduction in first-pass metabolism and the efficient transfer of high medication doses to the lymphatic system.

Due to their roles in both transport and immunomodulation, lymphatic vessels have become a focus in therapeutic design. Following noninvasive oral or intradermal/subcutaneous distribution, lymphatic vessels can effectively facilitate immunomodulatory treatments, thereby enhancing the efficacy of therapies requiring access to lymph nodes for optimal effectiveness. Although there has been some progress in understanding how to target lymphatic transport, the precise methods to target specific immune cell populations after their transportation to the lymph nodes remain not fully comprehended.

Lipid-based formulations will also continue to change the face of oral peptide and protein medication delivery, capitalizing on current advancements in the field and exploring potential avenues for future development.

With the discovery of more lipophilic drug candidates, there is a growing interest in formulation design strategies aimed at optimizing lymphatic transport. Stimulating intestinal lymphatic transport offers potential benefits, including the reduction of first-pass metabolism and the delivery of high drug concentrations into the lymphatic system. While numerous studies have contributed to a deeper understanding of the role of lipid precursors in lymphatic drug transport and the development of diverse formulations, our comprehension of drug delivery via the lymphatic route at the cellular level remains limited. Consequently, to enhance the utility of intestinal lymph as an alternative mode of transport to the systemic circulation, further research is imperative. This research should focus on elucidating the underlying mechanisms of lipoprotein and drug binding in intestinal cells, as well as the impact of lipids and formulation excipients on this intricate process.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest All authors (So-Jeong Joeng, Woo-Yul Song, Chun-Woong Park, and Dong-Wook Kim) declare that they have no conflict of interest.

Research involving human and animal rights This article does not contain any studies with human and animal subjects performed by any of the authors.

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