MEDDOCS Open Access Publisher

ISSN: 2578-8760

Journal of Nanomedicine

Open Access | Review Article

Lymphatic *versus* Portal Drug Delivery: An Understanding of Drug Oral Absorption and Food Effect

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Received: Apr 23, 2025

Accepted: May 09, 2025

Published Online: May 16, 2025

Journal: Journal of Nanomedicine

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Lipid nanoparticles; SEDDS; Lymphatic absorption; Portal absorption; Drug transport pathways; Poorly soluble drugs; Oral bioavailability; Solubilization technologies; food effects; GMP manufacturing.

Introduction

As more new chemical entities are discovered with poor solubility and bioavailability, the applications of novel excipients and delivery technologies and their mechanisms by which the drug molecules are absorbed into systemic circulation, have been subject of continued interest [1]. Oral low bioavailability of drugs stems from low solubility, poor permeability, enzymatic degradation in stomach and GI tract, and the hepatic first pass metabolism [2]. The first pass metabolism remains one of the main impediments for enhancing absorption and bioavailability of many drugs. Even though there is a lot known about first pass (pre-systemic) metabolism, there are still reasons not clearly understood, especially, how the lymphatic pathway absorption impacts on the oral bioavailability. Furthermore, other impediments also include P_{pg} transport pumps and limited permeability across intestinal lumen in the GI tract. To by-pass first pass metabolism for enhancing the absorption of lipophilic drugs, lipids have been used to increase the oral bioavailability via intestinal lymphatic system as shown in Figure 1 [3].

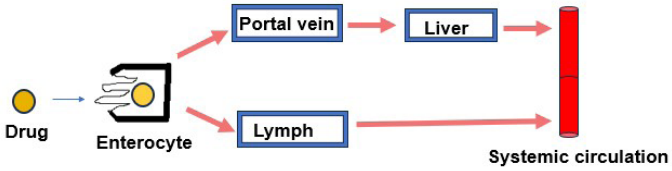

Figure 1: Pathways for drug transport via Portal vein and Lymph.

Cite this article: Ali S, Huang J. Lymphatic *versus* Portal Drug Delivery: An Understanding of Drug Oral Absorption and Food Effect. J Nanomed. 2025; 8(1): 1072.

These two pathways, upon molecules transit across the enterocytes in epithelial cell, play an important role for drug absorption; one where the molecules enter blood capillaries through the portal vein, and the other one by lymph capillaries through the lymphatic system. Soluble, small molecules preferably transported through the portal vein and get metabolized, leading to lower concentrations in the plasma. Lipophilic drugs with logP >5, on the other hand, are preferentially transported through intestinal lymphatic system that leads to greater absorption and bioavailability. The greater association with lipoproteins and chylomicrons assemblies due to inherent lipophilicity of molecules gets into enterocyte and transported to plasma through intestinal lymphatic system. Less lipophilic molecules with logP <5 get transported via portal system. For example, macromolecules like insulin and GLP-1 are preferably transported through the portal vein (Figure 1).

The lymphatic system is network of capillaries and small vessels, nodes and organs, that is filled with fluids that play an important role in modulating immune functions as well as also help facilitate the lipid absorption, a key mechanism to overcome the portal absorption and by-pass the first metabolism in liver. This distinctive route is essential for drug transport and delivery of large and lipophilic molecules by alleviating the challenges in penetrating blood capillaries. Composed of single layer of epithelial cells, filled with interstitial fluids, these capillaries are distributed throughout the body, that allow the entry of dissolved substance into lymphatic system that enter bloodstream via drainage and filtration of lymphatic fluid into lymph nodes. The filtration of lymphatic fluid eliminates bacteria, viruses or any other foreign particles. Lymph nodes are important in fighting envision of foreign particulates and help protect the immune response by triggering the lymphocytes to produce antibodies to fight infections.

Lipid nanoparticles

Lipid based formulations, comprised of lipid aggregates with varied in structure and compositions, are one of the important routes for delivery of drugs though lymphatic systems to bypass the liver metabolism. Designed to enhance solubility and stability, the lipid assemblies protect drug from degradation as they transit through GI tract. These lipid aggregates are further categorized as liposomes, solid nanoparticles, nanostructured lipid carriers, cubosomes, Self-Emulsifying Nano- and Micro-emulsions (SNEDDS/SMEDDS). Drugs with higher logP have shown higher solubilization than those with lower logP by this formulation approach [4]. Lipophilic drugs dissolved in SNEDDS does not necessarily improve the absorption. In fact, lipid suspensions have also shown the improvement of bioavailability of drugs like griseofulvin, and others [5]. Like lipids, proteins also play an important role in enhancing oral bioavailability by lymphatic pathway. Proteins engineered with certain receptors can target lymphatic endothelial cells, and hence, allowing more uptake by lymphatic system. For instance, albumin and Immunoglobin G (IgG) based nanoparticles can lead to improved stability and controlled systemic release due to lymphatic absorption as well. Conjugation of drug with proteins can lead to improved pharmacokinetic properties by facilitating the interactions with lymphatic transporters and receptors and enhancing the drug accumulation in the lymphatic tissues.

There are several approaches to increase drug transport to lymphatic system [3].

1. Postprandial state – a diet-based inclusion of drug with food
2. Lipid prodrug- drug is covalently linked with lipid moieties like long chain fatty acids, glyceride and phospholipids making drugs to be more lipophilic
3. Lipid Nanoparticles (LNPs) – administration of drug with lipid-based assemblies comprised of lipids, solubilizers and/or surfactants can lead to significant lymphatic transport of drugs

In postprandial state, the chylomicrons level increases after consuming fatty foods with increased lipoproteins synthesis in the lymphatics. For example, halofantrine, an antimalarial drug, when administered with food in postprandial state, increased the lymphatic uptake in dog by 54% as opposed to only 1.3% increase in fasted state [6]. Like postprandial, lipid conjugates with covalently liked drugs, making the drug more lipophilic, result in association with lipoproteins/chylomicrons that leads to faster uptake by lymphatics and greater bioavailability. For example, valproic acid conjugated with phospholipids, especially with longer fatty acid lipids, shows greater association with chylomicrons and absorption in enterocytes leading to higher bioavailability as compared with short chain lipids [7]. Mefenamic acid modified with glycerides as prodrug, also shows higher plasma concentration as compared to free drug, suggesting that lipid prodrugs increase bioavailability and reduce the adverse effect in GI tract [8].

Role of lipids in lymphatic drug transport

Lipid Nanoparticles (LNPs) improve the stability of drug by encapsulating into interior aqueous and hydrophobic bilayers. Comprised of different class of lipids, short and long chain phospholipids, the liposomes or different lipid assemblies protect drugs from harsh conditions in the GI tract and minimize the degradation by enzymes. Phospholipids (and cholesterol) are digested in the intestine. Once the bile salt is released into the small intestine, phosphocholines are hydrolyzed to lyso-phospholipid and fatty acids by Phospholipase A_2. Thus, drugs like cefotaxime incorporated in liposomes are stable, and showed higher concentrations in lymph and plasma as compared to solution state, further supporting the fact that lymphatic transport play an important role in increasing the oral bioavailability of this drug [9]. Surface modified liposomes containing cyclosporine A with a positive charged stearyl amine showed better muco-adhesion than chitosan and much higher lymphatic absorption [10].

Lipophilic drugs solubilized in lipids are transported through lymphatic system via association with chylomicrons, a group of lipoproteins that comprised of triglyceride (85-92%), phospholipids (6-12%), cholesterol (1-3%) and proteins (1-2%). These lipoproteins complexed with hydrophobic lipids help to accumulate in the enterocytes before transported to lymphatic system and into the systemic circulation [3]. Lipids varied with fatty acids and degree of saturation determine the transport pathway. For instance, long chain triglycerides (oils) and fatty acids with C14 carbons or more are transported via lymphatic pathway, while with short chain lengths and less lipophilic are transported via portal vein. The longer fatty acids with unsaturation are prone to lymphatic pathway for transport to plasma. The unsaturated and longer fatty acids get accumulated as large chylomicron entities comprised of triglycerides, cholesterol esters and phospholipids, which are wrapped within lipoproteins before entering the intestinal lymphatic capillaries and eventu-

ally in systemic circulation [11]. Co-administration with lipids can increase the drug transport through intestinal lymphatic system. Upon hydrolysis of lipids, Fatty Acids (FA), Monoglyceride (MG) and bile salts form mixed micelles with drugs, which are taken up by enterocytes and undergo lymphatic transport in association with chylomicrons. On the other hand, the free molecules get transported through portal vein.

In spite of good understanding that lipid-based carriers promote lymphatic transport and increase systemic bioavailability, how other transport mechanisms impact on drug transport via chylomicrons movement within the cells remain the subject of continued investigation. Raloxifene encapsulated in Solid Lipid Nanoparticles (SLNs) showed 34% and 29% decrease in C_{max} and AUC on blocking the Chylomicrons (CM) flow by cycloheximide [12]. Likewise, there was considerable inhibition of C_{max} and AUC for liposomal carvedilol formulation by cycloheximide, suggesting the involvement of CM mechanism or pathway in contribution to overall oral bioavailability [13]. Other mechanisms such as M cell uptake pathway by accumulation in Peyer's patches could play an important role in transporting the drugs to systemic circulation via lymphoid tissues. The factors affecting the M cell uptake include particle shape and size, surface charge and surface hydrophobicity among others. With regards to size of polymeric nanoparticles, studies suggest that in oral administration, larger particles with 600 nm to 2000 nm are preferentially transported through lymphatic pathway than those <200 nm [14]. With oral nanocrystals, on the other hand, the larger particles 550-1100 nm are taken up by M cell and retained in Peyer's patches in the lymphoid tissues of the gut. They allow slower dissolution rate as compared to smaller particles (<280 nm). Bacchav et al. have demonstrated the uptake of rifampicin nanoparticles by Peyer's patch in smaller intestine of rats for targeted delivery to lung from a formulation comprised of a hydrophobic and mucoadhesive ethyl cellulose through lymphatic system by minimizing the hepatic exposure [15].

In addition to CM and M cell pathways, the paracellular and transcellular pathways also play an important role in enhancing oral bioavailability through lymphatic transport [16]. Of all four known pathways, lymphatic pathway remains most viable transport mechanism followed by the M cell pathway.

Table 1: Shows the contribution of intestinal lymphatic transport in improving the bioavailability of a few representative drugs [16].

Model drug	Technology	Results	Reference
Testosterone	Conjugation with C-9 fatty acid	Ab. oral bioavailability >3% with >90% lymphatic transport	17
Docetaxel	Conjugation with oleic acid	Over 2-fold higher BA than unconjugated drug in SNEDDS	18
Nitrendipine	SLN	BA >3-fold higher than suspension	19
Carvedilol	Microemulsions	BA >3% higher than solution	20
Olanzapine	NLC	BA >5% vs suspension	21
Lopinavir	Mesoporous silica	C_{max} 1.69-fold and AUC 5.97fold increase vs free drug	22
Probucol	SNEDDS	BA >10-fold improvement	23
Baicalin	Nanoemulsions	BA >26% and AUC 14.6-fold increase	24
Lutein	SMEDDS	Enhance lymphatic transport efficiency	25
Hepatitis B surface antigen (HBsAg)	PLGA coated with lectin	Higher anti-HbsAb antibody levels and enhanced mucosal immunity	26
Hepatitis B surface antigen (HBsAg)	Liposomes	Comparable IgG level with IM following immunization for 3 consecutive days	27

As shown in Figure 1, the first-pass metabolism is the result of efficient uptake and hepatic metabolism of drugs by liver. The blood filters through the GI tract and is collected in the portal vein and then passes through liver where all substances get absorbed with blood and distributed to other organs. To circumvent the passage through port vein and divert to lymphatic system, structural modifications are commonly practiced for improving the oral bioavailability. As shown in Table 1, testosterone's oral bioavailability is low, but on modification as prodrug with a fatty acid (undecanoic acid), oral bioavailability improved about 3% resulting from >95% contribution from lymphatic transport [17]. Docetaxel modified with oleic acid also showed about 2-fold increase in oral bioavailability in SNEDDS formulation as compared to unconjugated drug [18].

Food effect on drug transport

Food effect also known as food-drug interaction, plays an important role in determining efficacy and bioavailability of drugs. This is clinically relevant, specifically, in cases to prevent the undesired adverse effect and reduce drug overdosing. A majority of compounds are prone to food effects belong to BCS class II and/or Class IV, especially the positive food effect. Only a few have shown the negative food effect. A typical dosage is susceptible to fed and fasted state. Increasing plasma concentration of a drug with food (low or high fat diets) is referred to as positive food effect, while lowering plasma concentration of a drug with food referred to as negative food effect, as shown in Figure 2 [28].

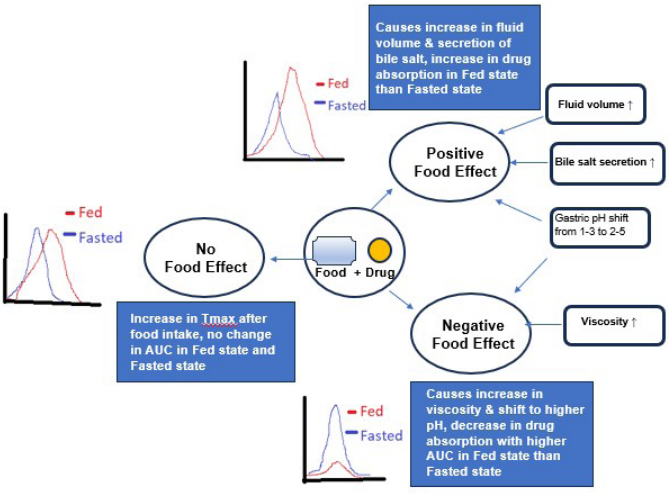

Figure 2: Illustration of food effects on absorption of drugs.

After consuming food, the gastric pH is raised from about 2 to 4 and remains elevated about 4.5 hours. As the food travels in duodenum and small intestine, the pH does not fluctuate as much as stomach and remains around 6-8. Fluid volumes could

elevate in stomach to 500 ml or higher and in small intestine may increase from 200 ml to 1000 ml. The solubility of drugs is increased by bile salts secreted from gall bladder. In addition, increasing in viscosity could hamper the release of drugs, making them less available for systemic absorption. Drug absorption is also affected by inhibition of transporters. For example, grapefruit juice when co-administered with drug leads to higher bioavailability due to inhibition of cytochrome P450 3A4. On the other hand, with lipophilic molecules, the lymphatic uptake route leads to increasing the bioavailability with fatty food diet.

Ivacaftor (MW 392.49), a cystic fibrosis approved drug is taken with food to maintain the bioavailability to 2.5-4 times, and hence, it shows a positive food effect. This is due to micellization of drug from oil and fat in food, longer residence time in the stomach, which leads to increasing drug absorption and reducing the hepatic first pass metabolism [29]. This study demonstrates that using polysorbate/Transcutol (2:1) in combination with a novel oil in SNEDDS formulations, Ivacaftor is very stable, and rapidly dispersed in water, and pH 1.2 and 6.6 buffers and yields an average particle size of 75 nm regardless of varied dilutions. In vivo studies of ivacaftor in SNEDDS in beagle dogs eliminates the food effect and the oral bioavailability remained 150% or higher in fed and fasted states (AUC remained similar in fed and/or fasted) as opposed to fed state suspensions. Thus, LNPs further confirmed the improved therapeutic efficacies and bioavailability via lymphatic system and devoid of hepatic first-pass metabolism [30].

There are also interests to find the appropriate formulations with lesser degree or no dependent upon foods, and to reduce the subject variabilities and to meet the patient compliances. Miao et al. investigated the lipid based self-nanoemulsifying system (SNEDDS) to reduce food and patients' variabilities without affecting the oral bioavailability of drug. Using a bi-functional novel oil in SNEDDS formulation comprised of solubilizer and co-solubilizer, it resulted in fine droplet of nanoemulsions with particle size ranging 5-100 nm in GI tract [31]. Like Ivacaftor, other BCS class II and IV drugs like itraconazole, torcetrapib and ziprasidone have shown reduced food effects in SNEDDS formulations [32-34. It is evident from studies that maximum solubility of these drugs in triglycerides or oil phase is critical to help self-emulsify and protect the drug in hydrophobic interiors to reduce food effect. Venetoclax, a BCS Class IV lipophilic drug with log P of 8 drugs has the positive food effect and on co-administering with high fat meal showed higher bioavailability due to lymphatic uptake [35,36].

Negative food effect is as the result of increasing viscosity following food consumption which in turns an impediment in dissolution/disintegration due to lower water penetration, causing a lesser degree of absorption and leading to significant decrease in the bioavailability of drug. For BCS class I drug like Zolpidem, showed a negative food effect, an anomalous behavior than other Class I drugs as evident by its decrease in C_{max} and increased in T_{max} and hence, yielded a lower bioavailability with food consumption [37,38].

For example, lopinavir/ritonavir (Kaletra®), available as tablets and comprised of copovidone do not show any food effect while the soft gel capsules comprised of polyoxyl 35 castor oil (Kolliphor® EL) and oleic acid, showed the food effect. The food effect in soft gel lipid-based excipients further suggest that these drugs are absorbed through lymphatic system rather that hepatic portal system [39]. Cannabidiol, a lipophilic drug with logP 6.3, undergoes extensive first pass metabolism in liver and also transported through intestinal lymphatic system in blood with high fat food [40]. Thus, lipid-based excipients and solubilizers in formulations can lead to diversion of drug to avoid first pass and to direct an increase of drug concentration in plasma via lymphatic system.

Table 2: Shows a number of oral drugs are also subjected to variabilities in BA when taken with food, especially, in fasted state or fed state with low fat or high fat diets [41].

Drug/ BCS Category	Route	Indication	Recommendation	Reference
Albendazole/II	Oral	Anthelmintic	Taken with meal	42
Ampicillin/III	Oral	Antibiotics	Taken 1 h before and 2 h after meal	43
Nelfinavir/II	Oral	Oncology	Taken with food	44
Posaconazole/II	Oral	Antifungal	Taken with food within 20 min after meal	45
Mefloquine/II	Oral	Antimalarial	Taken after the meal	46
Norfloxacin/IV	Oral	Antibiotic	Taken 1 h – 2 h before meal	47
Capectabine/I	Oral	Oncology	Taken with food or within 30 min after meal	48
Didanosine/III	Oral	Antiviral	Taken in empty stomach or within 30 min before or 2 h after meal	49
Misoprostol/I	Oral	Prostaglandin	Taken with food to reduce side effects	50
Glipizide /II	Oral	Hypoglycemic drug	Taken 30 min before meal	51
Cyclosporine/II	Oral/IV	Immuno-suppressant	Food variabilities	52
Isoniazide/I	Oral/IM	Tuberculosis	Taken empty stomach 1h before or 2 h after meal	53

As evident from Tabel 3, many drugs are food dependent, and also majority belong to Class II with some Class IV, and also Class I, and Class III. They are also recommended to be taken with and without food and/or in an empty stomach before the meal. Take collectively, the food effects on drug absorption can neither be avoided nor exploited. Undesirable food effects can lead to exposure and increased toxicity or reduced therapeutic efficacy. Hydrocortisone, for example, when taken with food leads to delayed release by reducing C_{max} and prolonged T_{max} as opposed to fasted state. Therefore, hydrocortisone should be taken with empty stomach before breakfast and to be more clinically relevant [54]. On the exploitation, co-administration with food is required to increase solubility and absorption of drugs and to achieve the desired bioavailability. For example, rivastigmine when taken with food, led to 30% AUC and 30% decrease in C_{max} with 1.5 h delay in T_{max} to achieve the desired

bioavailability [55]. In many cases the food intake is required and recommended to prevent the adverse effects such as gastric irritation, bleeding, nausea among others, which are all clinically relevant.

Conclusion and future perspectives

Lymphatic absorption remains as an alternative and an ideal approach to enhance the oral bioavailability of poorly soluble molecules, specifically, those belonging to BCS II and IV. As many of the molecules discovered today are poorly soluble, making them oral bioavailable by using the conventional technologies like pH change and salt formation and micronization might not be the appropriate routes. Further, challenges associated with hepatic first pass metabolism undermines the absorption and bioavailability of molecules in both conventional and innovative formulation technologies such as polymeric and lipid nanoparticles. Therefore, we expect more molecules being discovered will be utilizing the lymphatic system *versus* portal system for delivery of poorly soluble and permeable drugs to target sites. Chylomicron (CM) and M cell pathways will likely lead the way for transporting of these molecules based on physico-chemical properties such as particle size and shape, ionic charges, viscosity as well as the excipients including polymers and solubilizers and lipid-based oils and surfactants when used in formulations. Though M cell presents the main conduit in GI tract, lack of efficient passage due to limited population of M cell in the enteric epithelium makes the CM viable route of lymphatic and systemic circulation by enabling enteric lymphatic transport.

Food intake can impact drug transport and may divert the transport via lymphatic or portal vein or could be preferential favoring one over other. There are no obvious reasons to believe which of the 2 transport routes will be preferred and to what extent it will be impacted. There are pharmacokinetic models to evaluate the food effect on bioavailability of drugs. Lower absorption and bioavailability are taken as markers for hepatic first metabolism, as shown in Figure 3 [56].

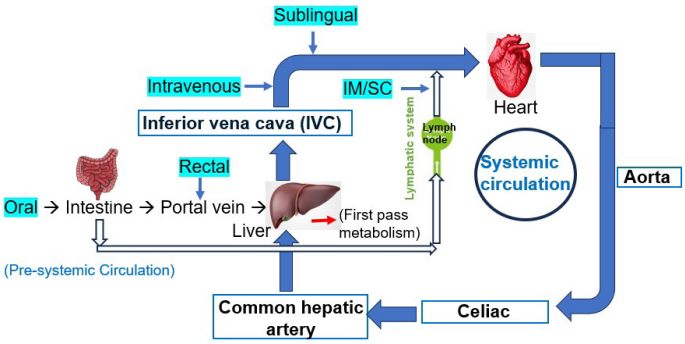

Figure 3: Illustration of first pass metabolism and systemic circulation routes.

Will that change with food, high or low-fat diet? Most likely, and it all depends on the drug molecules and dosages, and the ingredients used in the formulations. As evident in Figure 3, IM, SC and sublingual routes will bypass the hepatic metabolism without going to digestion in stomach. Food digestion in stomach, viscosity, and its retention for 1-4 hour, before existing to duodenum and reaching to enterocytes in the epithelium cells of the GI tract, will all impact the C_{max}, AUC and T_{max} of a drug molecule. Drug particulates with smaller in size will have lesser challenges in absorbing through epithelium via lymphatic system and will have lesser food effect as opposed to larger particulates, and those most likely will go through portal vein in liver, leading to lesser degree of absorption and low bioavailability.

Ascendia's enabling technologies (LipidSol™, EmulSol®, NanoSol®, and AmorSol®) offer a range of formulation choices to design better and smarter dosages, oral liquids and solids, to mitigate the food effect and improve the oral bioavailability by finding the appropriate class of lipids and surfactants, and oils to achieve the desired outcomes. This is essential and required for new chemical entities with solubility challenges and for improving their bioavailability by directing them to lymphatic pathways (Chylomicrons and M cells).

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