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Review

Liposomal formulations for enhanced lymphatic drug delivery

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ABSTRACT

The lymphatic system that extends throughout the whole body is one of useful targets for efficient drug delivery. The intestinal lymphatic drug delivery has been actively studied to date because administered drugs can avoid the first-pass metabolism in the liver, resulting in improvement of oral bioavailability. Drugs must be hydrophobic in order to be transported into the intestinal lymphatics because the lipid absorption mechanism in the intestine is involved in the lymphatic delivery. Therefore, various lipid-based drug carrier systems have been recently utilized to increase the transport of drug into the intestinal lymphatics. Lipidic molecules of the lipid-based drug delivery systems stimulate production of chylomicrons in the enterocytes, resulting in an increase in drug transport into lymphatic in the enterocytes. This review summarizes recently reported information on development of liposomal carriers for the intestinal lymphatic delivery and covers important determinants for successful lymphatic delivery.

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1. Introduction

Lymphatic drug delivery is receiving increasing attention because of its many advantages over other routes. This attention has included a number of trials evaluating transport of drug to the lymphatic system. Various lipid-based nano-carriers have been developed to selectively utilize the lymphatic system for drug delivery. In this review, we will summarize recent advances in developing novel liposomal

drug delivery systems suitable for the targeting of drug to the lymphatic pathway.

2. Overview of intestinal lymphatic drug transport

The lymphatic system is a drainage network that extends throughout the entire body in proximity to the circulatory

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system. It returns lymph, a colorless fluid containing proteins, sugar, oxygen and lymphocytes that have leaked into the interstitial space, to the blood. The intestinal lymphatic system also contributes to the absorption of products from lipid digestion such as long chain fatty acids and lipophilic vitamins. In addition, the lymphatic system transports various immune cells and other elements essential to immune system function.

From the point of view of drug delivery, the lymphatic system is a very attractive target since orally administered drugs can work more effectively when transported selectively to the intestinal lymphatic system. Various drugs that are absorbed from the intestine into the systemic circulation have poor oral bioavailability due to degradation of active drug in the gastrointestinal tract prior to absorption. The pH of stomach fluid may range from 1.0 in the fasted state to 3.0–4.0 in the fed state and this extremely acidic environment facilitates the degradation of orally administered drugs. Moreover, before entering the systemic circulation, drug absorbed into the portal venous system undergoes first-pass metabolism in the liver. This results in a lower bioavailability and plasma concentration of the drug.

On the other hand, highly lipophilic drugs that have a $\log P > 5$ and a long-chain triglyceride (TG) solubility > 50 mg/g will transit across the enterocyte and associate with enterocyte lipoproteins to form chylomicrons [1]. These chylomicrons and the associated drugs then enter the mesenteric lymph duct, move to the thoracic duct, and finally enter the systemic circulation at the junction of the left jugular and the left subclavian veins. As a result of this anatomy, highly lipophilic drugs can avoid hepatic first pass metabolism.

The bioavailability of drugs that undergo significant first-pass metabolism in the liver can be improved by utilizing the lymphatic system for absorption in the intestine, thus avoiding the first-pass effect in the liver. Additionally, toxicity profiles of drugs can be changed since drug concentration and persistence in the lymphatic system and systemic circulation will be influenced by the dynamics of intestinal lymphatic transport [2].

Furthermore, the lymphatic system can be a target for treatment of other diseases such as acquired immune deficiency syndrome (AIDS) and cancer. Human immunodeficiency virus (HIV), which causes AIDS, colonizes lymphoid organs such as the spleen, thymus and lymph nodes. In the early stage of infection and throughout the latent stage, the virus replicates vigorously in lymphoid organs, meaning that lymphatic drug delivery can be advantageous in the treatment of AIDS [3]. The lymphatic system also contributes to metastasis of certain cancers. Because lymphatic vessels have pores for entry and exit of immune cells, tumor cells can easily enter the vessels and move to distant organs resulting in metastasis. Therefore, if chemotherapeutic drugs can be targeted to the lymphatic system it may be possible to inhibit the metastasis of solid tumors [4–7].

To transport drugs to the lymphatic system via the intestine, specific physiological conditions should be established. That is, lymphatic drug delivery depends on the physiological processes of lipid digestion and absorption. The lipid digestion and absorption process associated with the lymphatic delivery of lipophilic drugs has been extensively reviewed [8–10]. For example, in the case of the lipophilic antimalarial drug halofantrine ($\log P$ 8.5, TG solubility > 50 mg/ml), the

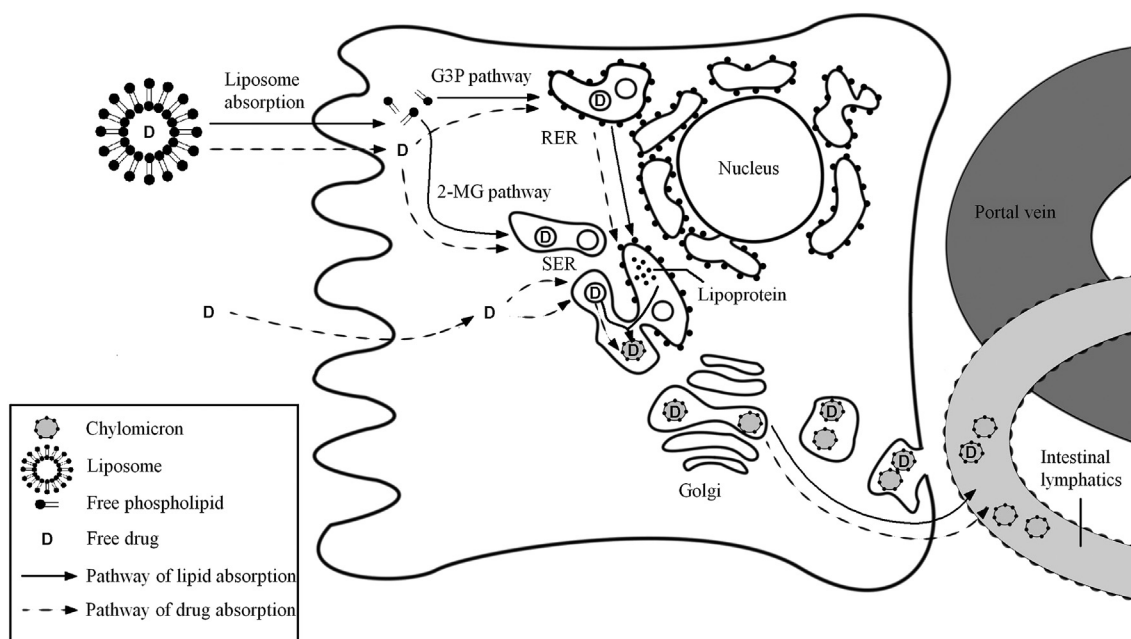


Fig. 1 – A mechanistic model of the absorption pathway of drug-encapsulated liposomes via intestinal lymphatics. Free phospholipids from liposomes are utilized to stimulate production of chylomicrons by the G3P pathway on rough ER, and the 2-MG pathway on smooth ER. Drug associated with CM is expected to enter intestinal lymphatics. This figure has been modified from reference [2].

degree of lymphatic transport was strongly correlated with the TG content of the lymph [11]. This suggests that lipid digestion products are needed to stimulate the production of chylomicrons. Thus, several types of lipid-based nanoparticles can be employed to mimic the physiological conditions favorable for lymphatic drug delivery.

2.1. Lipid-based nanoparticles as intestinal lymphatic drug delivery systems

As shown in Fig. 1, the co-administration of drug with a lipid-based formulation stimulates enterocyte production of chylomicrons, which dissolve and load lipophilic drugs in their nonpolar core and thereby promote absorption into the intestinal lymphatics and organs. Therefore, lipophilic drugs are absorbed into the intestinal lymph by association with lymph lipoproteins [12,13].

Nanocarriers can be used to overcome many of the drawbacks of conventional dosage forms; their use might help to improve solubility and dissolution rate, increase bioavailability, protect sensitive drugs from degradation, and reduce side effects. Furthermore, this type of nanoparticle formulation raises the possibility of targeting specific biological sites either passively or actively. Unique features of nanocarriers such as size and lipophilicity can be taken advantage of to target drugs to specific tissues or organs like the liver or the brain. We can also deliver drugs to other specific sites or cellular targets by modifying their surfaces [14]. There exist several types of lipid-based nanoparticles we can use for this purpose (Table 1). As an informative figure, the structural drawing of lipid-based nanoparticles such as multilayer liposome, solid lipid nanoparticle, and self-microemulsifying drug delivery system can be seen in Fig. 2.

2.1.1. Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are lipid-based drug carriers that remain solid at room and body temperatures. Lipids utilized for SLNs are typically physiological lipids, including: fatty acids, steroids, waxes and mono-, di-, or triglyceride mixtures. SLNs are composed of a lipid core that stimulates formation of chylomicrons, which transport the carrier and associated drug via the classical transcellular mechanism of lipid absorption [12]. This process increases the absorption of drugs into the lymphatic system. SLNs also have the potential to allow: controlled drug release and drug targeting, increased

drug stability and high drug payload. They can be produced and sterilized in large quantities, can be used to deliver both lipophilic and hydrophilic drugs, and lack the biotoxicity of organic solvents. Additionally, SLNs are being used increasingly for the protection of labile drugs from degradation in the body and for sustained release [15,16].

Clozapine SLNs administered intravenously and intraduodenally showed increased bioavailability with an increase in (AUC) of 3 and 4.5 times, respectively, as compared to clozapine suspension. This increased AUC for SLNs could be due to avoidance of first pass hepatic metabolism by SLNs driven intestinal lymphatic transport. The positively charged clozapine SLNs showed increased bioavailability with an increase in AUC as compared to neutral charged clozapine SLN. This may be because positively charged particles are better taken up by intestinal lymphatics than neutral or negatively charged particles. Increase in chain length of triglycerides was also positively correlated with extent of lymphatic absorption of the clozapine SLNs [17]. Tobramycin, a drug that is not absorbed through the GI tract and is administered parenterally, was administered to rats duodenally in the form of SLNs resulting in 100 and 20 times higher AUC than IV-administered tobramycin SLNs and tobramycin solution, respectively. This difference between the two administration routes can be attributed to the transmucosal transport of SLN to lymph instead to blood [18]. These results indicate that SLNs could be a useful drug delivery system that improves the bioavailability of lipophilic drugs.

2.1.2. Self-nanoemulsifying drug delivery systems

Self-emulsifying drug delivery systems (SEDDS) are mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants used for the improvement of oral absorption of highly lipophilic drugs. Upon mild agitation followed by dilution in aqueous media, such as GI fluids, these systems can form fine oil-in-water (o/w) emulsions or microemulsions. Self-emulsifying formulations spread easily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. The oil represents one of the most critical excipients in the SEDDS formulation not only because it can solubilize marked amounts of the lipophilic drug or facilitate self-emulsification, but importantly because it can increase the portion of lipophilic drug transported via the intestinal

Table 1 – Lipid-based drug delivery systems studied for lymphatic delivery.

Delivery systems	Drug name	Remark	References
SLNs	Clozapine	BA from SLN > suspension	[19]
	Tobramycin	BA from SLN > solution	[20]
SMEDDS	Halofantrine	Lymphatic availability of 17.9%	[20]
	Raloxifene	Intestinal penetration ability of SMEDDS > suspension	[21]
	Vinpocetine	BA from SMEDDS > suspension	[22]
Liposomes	Cefotaxime	BA from liposomes > aqueous solution	[24]
	(+)-catechin	BA from elastic liposome > conventional liposome	[30]
	Cyclosporin A	BA from liposome with bile salt > conventional liposome	[33]
	Calcitonin	BA from carbopol-coated liposome > noncoated liposome	[35]
	rhEGF	BA from PEG-coated liposome > DPPC liposome	[38]

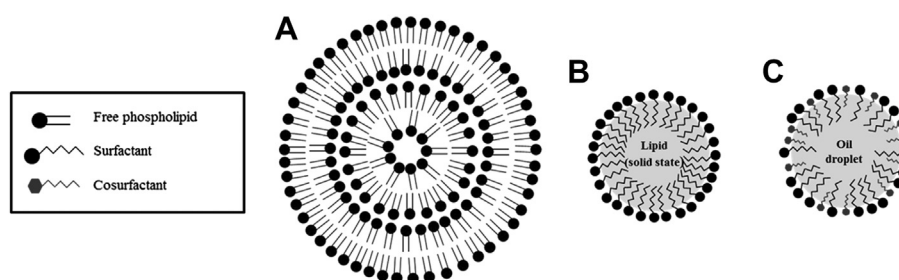


Fig. 2 – A structural drawing of multilayer liposome (A), solid lipid nanoparticle (B), and emulsified oil droplet formed from self-microemulsifying drug delivery system (C).

lymphatic system. This results in increased absorption from the GI tract depending on the molecular nature of the triglyceride emulsion [19].

Oral administration of halofantrine SMEDDS used for treatment of malaria showed the lymphatic availability of 17.9% via the thoracic duct and produced a total bioavailability of 74.9% [20]. The raloxifene SMEDDS exhibited improved penetration ability compared to the plain drug suspension in the *in vitro* intestinal permeability studies. SMEDDS formulations of raloxifene are expected to improve the oral bioavailability as evidenced by the increased penetration ability of raloxifene SMEDDS. Although the exact mechanisms responsible for this improved absorption are not fully identified, the reasons for the enhancement of bioavailability would be stimulation of lymphatic transport due to the triglyceride core of chylomicrons [21]. Comparing with vinpocetine (VIP) crude drug powder and commercial tablets, negatively charged VIP-SMEDDS exhibited 3.4- and 2.9-fold increase, respectively, in the percent of accumulated dissolution at 3 h. Relative bioavailability of negatively charged VIP-SMEDDS and positively charged VIP-SMEDDS increased by 1.85- and 1.91-fold, respectively, in relative of VIP crude powder suspension. The reasons for enhanced bioavailability of VIP would be contribute to the improved release, enhanced lymphatic transport, and increased penetration ability of VIP-SMEDDS [22]. These results indicated that the S(M)EDDS is potentially a good drug delivery system for oral delivery of the hydrophobic drugs.

2.1.3. Emulsion

Emulsions are heterogeneous delivery systems generally consisting of a dispersed phase and a continuous phase with the interface between them. In oil-in-water emulsions, the oil is dispersed as droplets within an aqueous phase. Water-in-oil emulsions are also possible. Emulsions with droplet sizes <100 nm are called microemulsions and are thermodynamically stable systems. Microemulsions are systems consisting of water, oil, surfactants and cosurfactants, and they have the capacity to solubilize both water-soluble and oil-soluble drugs. Emulsions and microemulsions can be used as carriers for drugs with poor water solubility, as sustained-release systems and as site-specific drug delivery vehicles by binding ligands for various cell-receptors to the particle surface [14].

Administration of a poorly water-soluble drug as an emulsion may improve bioavailability by eliminating a slow

dissolution step as a barrier to drug absorption, by enhancing intestinal lymphatic drug transport, or by a combination of both processes. Other potential mechanisms by which emulsions may enhance drug absorption include effects on gastrointestinal membrane permeability, transit time or on the metabolism of the drug [23].

2.1.4. Liposomes

A liposome is a vesicle containing a lipid bilayer composed of unimers that usually have a hydrophilic head and a hydrophobic tail and are oriented so that the hydrophobic head groups are inside the bilayer. Among the lipid-based nanoparticulate drug delivery systems potentially useful for efficacious lymphatic drug delivery, liposomes have received significant attention for its ability to enhance the permeability of drugs across the enterocyte, to stabilize drugs, and to provide the opportunity of controlled release [1]. For this reason, more about liposomal carriers as lymphatic drug delivery systems will further extensively discussed in the following section of the review.

3. Significance of liposomal carriers for intestinal lymphatic drug delivery

3.1. Improvement of stability and bioavailability of drug by liposomes

Liposomal drug carriers for oral administration were developed in the 1970s to protect labile drugs from denaturation by the acidic environment of the digestive system. The use of liposomal drug carriers resulted in decreased degradation rates and increased uptake of drugs.

For example, cefotaxime, a hydrophilic drug with poor bioavailability, was encapsulated in liposomal carriers to protect it from the effects of low pH and increase transport of the drug into the intestinal lymph as well as its systemic bioavailability [24]. To evaluate drug-encapsulated liposomes for oral delivery of drugs with poor bioavailability, the authors compared three forms of the drug: a liposomal formulation, aqueous free drug, and a mixture of the drug and empty liposomes. Oral bioavailability of the drug in the liposomal formulation and drug given with empty liposomes was 2.7-fold and 2.3-fold greater, respectively, than that of drug given in aqueous solution. They also reported that lymphatic

localization of the drug was considerably increased compared to the other formulations. Thus, liposomes can be used as drug carriers to increase the intestinal lymphatic transport and the oral bioavailability of hydrophilic drugs with poor bioavailability.

Since DNA vaccines are unstable after oral administration, an effective method is needed to improve their stability. Oral delivery of liposomes with entrapped DNA vaccines was reported by Perries et al. [25]. Their stability studies in simulated intestinal media revealed significant differences in excreted IgA levels between mice dosed with liposome-encapsulated DNA and mice dosed with naked DNA. The immunological response induced by liposomal DNA vaccines was bigger than that induced by naked DNA. This result could be attributed to the increased stability of distearoylphosphatidylcholine liposomes in the gut, resulting in the protection of DNA from nuclease, and to increased uptake by the gut lymphatic system. These experiments suggest that employing liposomal carriers for drugs given orally can increase DNA transport to the lymphatic system.

3.2. Improvement of penetration ability of liposomes across enterocytes

Encapsulation of drugs in liposomes alone cannot always achieve increased lymphatic transport. The ability of liposomes to penetrate biomembranes is important for lymphatic drug delivery. The nanoparticles must be small and deformable enough to cross biomembranes [26–28]. There have thus been several studies focused on the improvement of liposomal penetration for oral lymphatic delivery.

Hashida et al. studied the *in vivo* absorption characteristics of liposomes containing carboxyfluorescein as a model compound. They compared the plasma and lymph concentration of the released carboxyfluorescein to that of the free dye [29]. However, there was no significant difference between the concentrations achieved with the two formulations, indicating that the liposomes encapsulating the compound did not sufficiently permeate the intestinal mucosa. To overcome this limitation, they co-administered lipid-surfactant mixed micelles and the liposomal formulation. This resulted in enhanced penetration of drug-containing liposomes by the interaction between the lipid-surfactant micelle and the bilayer of the intestinal cell membrane.

There was also a trial of elastic liposomes measuring improvement of oral bioavailability of (+)-catechin [30]. The authors incorporated ethanol and a nonionic surfactant, Tween 80, into liposomes to increase their flexibility. Ethanol and Tween 80 influence the phosphatidylcholine bilayers of liposomes by increasing the environmental heterogeneity of phospholipids [26–28]. They also reported that incorporation of the compounds into nano-sized liposomes can increase the lipid surface area and consequently the bioavailability compared to simple liposomes. The bioavailability of the compound and the stability of the liposomes stored in simulated GI fluids both improved with addition of Tween 80 and ethanol.

Bile salt was also tested to see if it improved liposomal penetration of biomembranes. Bile salt-stabilized vesicles (bilosomes), which have shown potential in oral vaccine

delivery [31–33], may both protect antigens from the hostile environment of the GI tract and improve transmucosal uptake and immunization [32]. Bilosome-encapsulated cyclosporin A (CyA) showed superior oral bioavailability due to enhanced penetration of the bilosomes [34]. The CyA-encapsulated bilosomes also promoted uptake by M-cells in Peyer's patches, and thereby increased absorption through the lymphatic system. Furthermore, the incorporation of bile salts into liposomes may stabilize the membrane against the detrimental effects of physiological bile acids in the GI tract [31].

3.3. Effect of liposomal surface charge on drug transport across enterocytes

Liposomal surface charge has been experimentally modified in attempts to increase drug transport to the intestinal lymphatic system. The residence time of the liposomal drug carrier in the GI tract influences drug bioavailability. In an effort to increase the GI residence time of the liposomal drug carrier, liposomal surface charge was modified by coating the liposomes with Carbopol and chitosan, thereby changing their mucoadhesive properties [35]. Negatively-charged carbopol (CP)- or positively-charged chitosan (CS)-coated liposomes encapsulating calcitonin showed a 2-fold increase in pharmacological efficacy over non-coated liposomes. The mucoadhesive properties of the CP- and CS-coated liposomes were measured by a particle counting method. The negatively charged CP-coated liposomes and the CS-coated liposomes had a higher adhesion percentage than positively charged liposomes, resulting in improved pharmacological efficacy [35].

In another trial investigating liposomal surface charge modification, CyA-loaded liposomes prepared with cationic stearylamine (SA), anionic phosphatidylserine (PS), and coated with CS were developed [36]. The authors evaluated the mucoadhesivity of the liposomes. Mucoadhesive tests using rat intestine showed that the best adhesion rate among the three formulations belonged to liposomes prepared with SA (liposomes prepared with PS: 56%, liposomes coated with CS: 61%). These results indicate that a positive surface charge on liposomal drug carriers could enhance intestinal lymphatic delivery.

Unilamellar dipalmitoylphosphatidylcholine (DPPC) liposomes with a negative surface charge are another vehicle developed for transport of antigens to stimulate an immune response [37]. The authors demonstrated M-cell uptake and a successful immune response in rats given these liposomes with a negative surface charge.

3.4. Liposomes with coating material for enhanced performance

Modified liposomes have been used to increase transport of drugs to the intestinal lymphatics. For example, polyethyleneglycol (PEG)-coated liposomes were developed to improve absorption of human epidermal growth factor (rhEGF), a single-chain polypeptide containing 53 amino acid residues and three disulfide bonds [38]. Although liposomes are useful carriers for intestinal lymphatic delivery of drugs, they are vulnerable to digestion by bile salts [39–41]. To

overcome this limitation, liposomes coated with polyethyleneglycol were created [39,40]. PEG-coated liposomes containing rhEGF were shown to have the potential to improve the GI stability and absorption of rhEGF [38]. The area under the concentration time curve was increased 1.7- and 2.5-fold by both phosphatidylcholine and DPPC liposomes, respectively. This increase in AUC is attributable to increased resistance to enzyme degradation and improved penetration of biological membranes.

Liposomes coated with proteins have also been produced. For example, liposomes coated with the reovirus cell attachment protein $\delta 1$, a ligand for receptors existing on M cells, were created [42]. These protein-coated liposomes had a 10-fold greater degree of association with rat Payer's patches after *in vitro* incubation at 4 °C for 1 h than did uncoated liposomes. This indicates that the protein-coated liposomes selectively adhered to the M cells and were thereby transported into mucosal lymphoid tissue, resulting in an enhanced immune response. This demonstrates the feasibility of targeting orally administered antigen for delivery to the lymphatic system via Peyer's patches.

3.5. Drug-related factors affecting the use of liposomal carriers

3.5.1. Physicochemical properties of drug candidates

The physicochemical properties of drugs critically influence the efficacy of oral delivery to the lymphatic system because these properties affect loading, or the concentration of drug per chylomicron. The two properties regarded as most important for loading of drug into chylomicrons are the partition coefficient and the TG solubility.

Affinity between drugs and TG is very important for lymphatic delivery. Charman et al. proposed that the partition coefficient and TG solubility of drug candidates should be $\log P > 5$ and >50 mg/ml, respectively [1]. They compared lymphatic transport of dichlorodiphenyltrichloroethane (DDT) ($\log P$ 6.19) with hexachlorobenzene (HCB) ($\log P$ 6.53) to dissect the importance of lipid solubility. Even though they have similar $\log P$ values, 33.5% and 2.3% of the administered dosage of DDT and HCB was transported to the lymphatic system, respectively. This result was attributed to the 13-fold difference in TG solubility between the two compounds [1].

However, the combination of a high partition coefficient and a high TG solubility is not sufficient for lymphatic delivery of drugs. In one trial, only 3% of administered panclomedine, an antitumor agent with $\log P$ of 5.48 and a TG solubility of 175 mg/ml, was transported to the intestinal lymph [43]. Similarly, CI-976, a lipophilic lipid regulator with a $\log P$ of 5.83 and a TG solubility of >100 mg/ml showed very poor transport with $<1\%$ of the dose reaching the intestinal lymph [44]. Furthermore, the authors reported a high level of lymphatic delivery of halofantrine hydrochloride Hf-HCl (43.7% of the dose). This degree of transport was similar to that of the lipophilic Hf presumably because of conversion of Hf-HCl to the lipophilic free base in the intestinal lumen [45].

Taken in totality, this research suggests that a drug's partition coefficient and TG solubility are important determinates of lymphatic transport. However, more research is

needed to establish with certainty all the factors important for successful lymphatic transport of drugs.

3.5.2. Prodrugs designed for enhanced lymphatic delivery

The lipophilicity of drugs can also be increased by attaching lipid molecules. Various lipid molecules such as a fatty acids, monoglycerides, diglycerides, or phosphoglycerides can be covalently bound to drugs to produce prodrugs. This approach is based on the fact that high lipophilicity is required for transport into intestinal lymph. An early attempt to increase the lipophilicity of drugs was a synthesis of simple esters by condensation with long-chain fatty acids.

For example, there was a trial to increase the bioavailability of testosterone. The absolute bioavailability of unmodified testosterone was approximately 4% due to first-pass hepatic degradation [46]. An absolute bioavailability of about 7% was achieved by attaching a lipid molecule to the hormone, producing a lipophilic ester prodrug [47]. In another study, epitiostanol, an anti-tumor agent, was modified by attaching 17-methoxycyclopentane ether to the drug producing an ether derivative of epitiostanol. The modified drug had superior bioavailability when compared with native testosterone [48–50].

This approach is limited by esterases and some peptidases existing in most organs of the body. Cleavage of ester bonds of prodrugs may occur before the prodrugs are associated with enterocyte-derived chylomicrons and arrest transit to the lymphatic system. Other approaches have been tried to overcome this limitation. As an advanced approach, prodrugs can be integrated into a biochemical pathway related to lipid processing. For example, glyceride-based prodrugs have been synthesized for integration into the lymphatic triglyceride absorption pathway [51–56].

Garzon–Aburbah et al. estimated the ability of diglyceride prodrugs of L-dopa and chlorambucil to be integrated into lymphatic triglyceride pathways [4,55]. L-Dopa is a drug that undergoes significant first-pass metabolism in the liver resulting in a low oral bioavailability. To transport this drug to the intestinal lymph, they attached palmitic acid moieties in the 1- and 3-positions and L-Dopa in the 2-position of a glycerol backbone. The 2-substituted L-Dopa derivative, which was a 2-monoglyceride mimic, is absorbed and integrated into the TG resynthesis pathway after the fatty acids covalently bound in the 1- and 3-positions are cleaved. 8.3% of the administered L-Dopa was present in lymph as the diglyceride prodrug, while 0.2% of the dose of the original L-Dopa administered orally was delivered to the intestinal lymphatic system.

In another study of the prodrug approach, a phospholipid-mimicking prodrug was produced. In the intestinal lumen phospholipids are hydrolyzed to lyso-phospholipids that are recycled after their absorption by enterocytes. Lymphatic delivery of fluorouridine, an anti-tumor agent, was attempted using this pathway [56]. The authors produced dipalmitoylphosphatidylfluorouridine (DPPF) as a phospholipid drug, and then analyzed thoracic lymph after oral administration. The concentration of DPPF-related congeners was approximately 30-fold larger than the plasma concentration of the prodrug, confirming that the prodrug was specifically transported to the intestinal lymph.

Despite several limitations such as labile linkages between drugs and lipid molecules, prodrugs can be a useful strategy for increasing the drug dose transported to the intestinal lymphatic system.

4. Conclusion and future perspectives

Various lipid-based nanoparticles for oral lymphatic delivery of drugs are increasingly being researched and developed. Liposomes containing entrapped drug are particularly useful nanocarriers that improve the oral bioavailability and efficacy of drugs by selectively utilizing intestinal lymphatic absorption, thus evading first-pass hepatic metabolism.

However, more research is needed to elucidate the mechanisms of selective transport of drugs to the intestinal lymphatics by liposomes, specifically processes at the cellular level including the digestion, uptake, and intracellular metabolism of the phospholipid from liposomes and drugs.

Moreover, the weaknesses of liposomes such as the stability of them in the stomach and the intestine also should be overcome to develop more advanced drug delivery system for the intestinal lymphatic delivery. Additionally, delivery of a broader range of candidate drugs having different physico-chemical characteristics such as hydrophilicity, hydrophobicity and instability in the GI tract must be tested. Further study of liposomes for lymphatic delivery is required not only to overcome these issues but also to develop more novel liposomal drug delivery systems for future uses.

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