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Nano-sized Drug Carriers and Key Factors for Lymphatic Delivery

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ABSTRACT − Specific diseases like cancer and acquired immune deficiency syndrome (AIDS) occur at various organs including lymphatics and spread through lymphatic system. Thus, if therapeutic agents for such diseases are more distributed or targeted to lymphatic system, we can obtain several advantages like reduction of systemic side effect and increase of efficacy. For these reasons, much interest has been focused on the nature of lymphatics and a lot of studies for lymphatic delivery of drugs have been carried out. Because lymphatics consist of single layer endothelium and have high permeability compared with blood capillaries, especially, the studies using nano-sized carriers have been performed. Polymeric nanoparticle, liposome, and lipid-based vehicle have been adopted for lymphatic delivery as carriers. According to the administration route and the kind of carrier, the extent of lymphatic delivery efficiency of nano-sized carriers has been changed and influenced by several factors such as size, charge, hydrophobicity and surface feature of carrier. In this review, we summarized the key factors which affect lymphatic uptake and the major features of carriers for achieving the lymphatic delivery. Lymphatic delivery of drug using nano-sized carriers has many fold improved ability of lymphatic delivery compared with that of conventional dosage forms, but it has not shown whole lymph selectivity yet. Even though nano-sized carriers still have the potential and worth to study as lymphatic drug delivery technology as before, full understanding of delivery mechanism and influencing factors, and setting of pharmacokinetic model are required for more ideal lymphatic delivery of drug.

Key words − Lymphatic system, Nano-sized carriers, Lymphatic delivery

The lymphatic system composing of circulatory system with blood circulating system has been observed since ancient times. As the functions of lymphatic system have been revealed by several groups in view of physiology and pathology, in the last few decades, the necessity of lymphatic targeting has been demanded (Swartz, 2001).

The lymphatic system has an important role in the maintenance of tissue fluid pressure homeostasis, in mediation of the afferent immune response via recruitment of immune cells like antigen presenting dendritic cells, memory T cell, and macrophage and soluble antigens toward draining lymph nodes where the immune responses are initiated, and in the intestinal absorption of dietary lipids. Furthermore, it is primary route for spreading cancer cells and disseminating infections. Once invaded by cancer cells or viruses, the regional lymphatics become roots for metastasis to other organs (Jurisic and Detmar, 2009; Cavanagh and Von Andrian, 2002; Chambers et al., 2002). Especially, lymph capillaries are larger than blood capillaries, and fluid flow rate is extremely slower. In addition, lymph fluid composition is very similar to that of interstitial fluid, which promotes cell viability. Therefore, the lymphatic system has been regarded as a great potential route for targeting delivery of drugs like anticancer drugs and immune modulating agents (Swartz, 2001). Moreover, as mentioned below, because the lymphatic system has specific anatomical features compared with blood capillaries, numerous studies have been performed for lymphatic delivery using drug nanocarriers including chemotherapeutic agents. The advantages of nanocarrier technology such as polymeric nanoparticles, lipid based nanoparticles, and liposomes are high stability, high loading capacity, ability to protect and to encapsulate hydrophobic and hydrophilic drugs, feasibility of variable administration routes, possibility to targeting, and control of drug release rate. Additionally nanocarrier system may improve drug bioavailability, reduce systemic side effects, and increase efficiency of drug therapies (Luo et al., 2010; Paliwal et al., 2009; Ling et al., 2006; Karajgi and Vyas, 1994; Parker et al., 1981). On the other hand, the studies that identify the important physicochemical factors affecting lymphatic delivery of carrier have been carried out. These factors include size, weight, charge, hydrophobicity, and surface feature (Rao et al., 2010; Kaur et al., 2008).

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In this review, the examples of nanocarriers and administration routes used to lymphatic delivery and the ideal physicochemical factors are discussed to efficient lymphatic drug delivery based on literatures. This review is divided into two sections. In first section, we described the structure and feature of lymphatic system and the physiochemical factor affecting lymphatic uptake according to administration routes. In later, we presented the character of each carrier and its efficiency of lymphatic delivery.

Administration Routes and Affecting Factors

Parenteral route

The carriers administered via parenteral routes like intramuscular, intra-venous, subcutaneous, and intra-peritoneal injection are directly absorbed to lymphatics with interstitial fluids. Briefly, the lymphatics comprise a one-way transport system for fluid and proteins by collecting them from interstitial space and returning them to the blood circulation. These compose five main categories of conduits whose size ranges from 10 μm to 2 mm in diameter. Specially, initial lymphatics that are located within the connect tissue have blind-ended or saccules structure (Swartz, 2001). Lymph capillaries are comprised of one layer endothelial cell, typically made up of one or two non-fenestrated and highly attenuated cells overlapped by other cells, with a discontinuous basement membrane. Overlapping interendothelial junctions function as valves with openings that are 10 to 25 nm wide, permitting the entrance of small particles. Otherwise, larger particles which cannot go through junctions are absorbed into the endothelial cells by pinocytosis (Tanis et al., 2001). Difference of pressure between luminal and interstitial space contributes to lymph formation. Lymph endothelial cells are linked to the extracellular matrix (ECM) by elastic fibers called anchoring filament. The link critically serves lymphatic function such as 'tissue pump' that creates oscillating pressure to lymph formation. It also preserves lymphatics by preventing vessel collapse. Lymph absorbed from interstitial space is moved to collecting vessel by systemic forces like respiration, blood pressure, exercise, and massage. It is passed through lymph nodes that function as filter, reservoir, and 'incubator' for white blood cell (Pepper and Skobe, 2003; Swartz, 2001).

Due to lymphatic properties as presented Fig. 1, macromolecules and colloids are absorbed through the opening and taken up by macrophages in lymph nodes. Therefore, nano-sized drug carriers can be used to target to lymphatic system and the lymphatic delivery of carriers is affected by several physicochemical factors, when drug carriers are injected. The

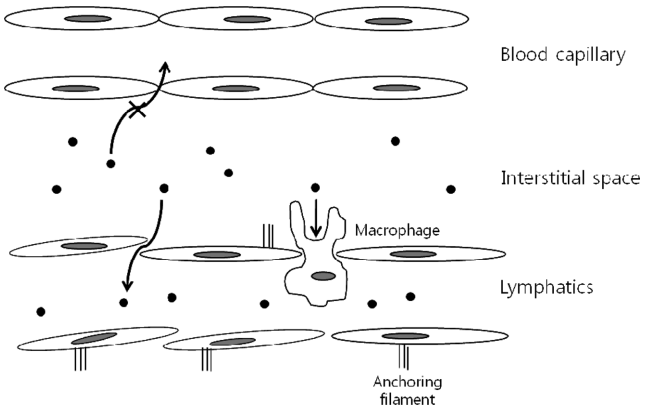

Figure 1. Schematic representation for the structure of lymphatics and mechanisms of lymphatic uptake of colloids and macromolecules (●). They are absorbed through the opening of lymphatics and taken up by macrophage in lymphatic system.

ability of carriers to flow into lymphatics is associated with carrier size, composition, charge, hydrophobicity, and surface feature. Indeed, the extent of lymphatic delivery could be enhanced by control of size, modification of surface, coating of polymers and adjusting of formulation. Especially, the molecular weight is very important factor for lymphatic delivery, and this has been reported by several researchers (Allen et al., 1993; Tumer et al., 1983). It was also reported that macromolecules with a molecular weight greater than 16 kDa have preferential lymphatic uptake. This finding was further supported by Takakura et al (Supersaxo et al., 1990; Takakura et al., 1984). They explained that molecular weight and size affect lymphatic delivery and retention in their study with mitomycin C conjugated with dextran (MMC, MMC-D). They prepared four formulations; free MMC, MMC-D (T-10), MMC-D (T-70), and MMC-D (T-500). After intra-muscular injection to rat, they observed lymphatic delivery and retention of formulations. Intra-muscular injection of MMC-D showed high concentration of MMC in lymph nodes. Specially, MMC-D (T-70) and MMC-D (T-500) which have bigger weight than others are more likely to uptake into regional lymph node. It indicated that relatively small and light carriers which are able to pass through blood capillary were not suitable for lymphatic delivery. Contrastively, once carriers were absorbed to lymphatics, the smaller carriers lead to better transfer with lymph fluid. The formulation which has smaller weight such as MMC-D (T-10) could be moved well through lymph flows (Takakura et al., 1984).

On the other hand, Oussoren et al (1997) claimed that size is the most crucial factor for lymphatic uptake of liposomes and determined that small liposomes, with a mean size smaller than 0.1 μm, were taken up into lymphatic capillaries to a high

extent, whereas lymphatic uptake clearly declined with an increasing mean liposome size, when liposomes were administered to subcutaneous injection. However, lymph node localization is much less dependent on liposome size. Lymph node uptake of small liposomes was found to be almost equal to the uptake of large sized liposome. The reason is that phagocytosis by macrophage was the most important mechanism of lymph node uptake and its in vivo capacity was limited and saturated. Also, in view of the outcome of in vitro studies on the interaction between liposomes and macrophages, lager liposomes may be phagocytosed more efficiently than smaller liposomes (Oussoren and Storm, 2001; Oussoren et al., 1997; Senior, 1987).

Another one affecting lymphatic delivery of carriers is surface feature. According to previous studies, mannose and lectin receptors are abundantly presented on the macrophage surface of lymphatic tissue, which enables to selective targeting by surface modification (Garg and Jain, 2006; Muller and Schuber, 1989). Hawley et al. studied about surface modification of nanospheres. In the study, they discovered that the movement of nanospheres into the lymphatic channels could be significantly modified by coating their surface with poly(L-lactic acid) (PLA): poly(ethylene glycol) (PEG). The enhanced movement of the nanospheres results in an increased number of nanospheres presented to the macrophages resident in the regional lymph nodes. At this moment, a balance in the properties of the surface between hydrophobic and hydrophilic character is required. Because, the nanospheres with steric barriers are demanded hydrophilic surface to drain from injection site, but still hydrophobic for providing opportunity of recognition to lymph node macrophages (Hawley et al., 1997). In the same manner, Kaur et al. performed study that is lymphatic targeting using surface-engineered liposomes for giving more affinity to macrophage. The surfaces of liposomes were engineered by stearylamine, dicetyl phosphate, and mannose for lymphatic targeting of zidovudine. In the organ distribution study, the subcutaneous administration of free zidovudine showed a very high concentration in the serum. However, it presented a poor organ distribution. Interestingly, a surface-engineered liposome exhibited significant reduction in free zidovudine concentration in serum, and significantly increased quantity of drugs was detected in the spleen and lymph nodes. It suggested enhanced uptake and localization of liposomes in the lymph nodes and spleen (Kaur et al., 2008).

Other important factor for lymphatic delivery of drugs embedded in carriers is surface charge. The surface charge effect of liposome on the targeting lymph and distributing tissue has been reported by several groups. However, it is not decided exactly what is the most efficient, positive, negative, or neutral (Kim and Han, 1995; Takakura et al., 1987; Patel et al., 1984).

In summary, when drug carriers were injected, the extent of lymphatic uptake is influenced by carrier size, molecular weight, and surface features. Carriers must have adequate and homogenous size, approximately ~70 nm, for uptake into lymphatics. Also, the lymphatic uptake may be elevated by modification of surface feature and hydrophobicity since carriers can be taken up into lymphatics by macrophage resident in the regional lymph nodes. Specific ligands interacting with receptor at macrophage could be attached to carriers and/or hydrophobicity of carriers could be controlled for increasing affinity of carriers about lymph node macrophage.

Enteral route

The intestinal lymphatic system is a specialized absorption and transport pathway for dietary lipids, lipid-soluble vitamins and highly lipophilic drugs. These lipophilic substances absorbed from GI tract drain into the mesenteric lymphatics and then, pass along a thoracic lymph duct, then join the systemic circulation at junction of the left internal jugular and left subclavian veins. Therefore, it can avoid hepatic first pass metabolism, which increases systemic absorption of drugs (Charman and Porter, 1996). Also, mentioned above, intestinal lymphatic system targeting can provide a number of advantages like supply of efficient way for anticancer, antiviral drugs, and immunomodulators and reduce of toxicity by local distribution of drugs.

Due to anatomical and physiological feature of intestinal lymphatic system, lipid based formulation is abundantly researched as drug delivery carriers. Possible mechanisms of intestinal drug absorption, using lipid-based formulations like liposome, solid lipid carrier, and lipid-cored carrier mimicking chylomicron (CM), are explained about four actions. These mechanisms are increasing of membrane fluidity, opening of the tight junction, inhibiting of P-gp and/or CYP450, and stimulating of lipoprotein and chylomicron production. The last mechanism is the most promising for intestinal lymphatic drug targeting using lipid-based carriers (O'Driscoll, 2002). When drugs are administered with lipid-based carriers via oral route, drugs and carriers are digested and changed to the absorbable forms by lipid digestion mechanism and taken up into enterocytes. Absorbed lipids like monoglycerides and fatty acids are resynthesised to chylomicrons by 2-monoglycerides pathway and gylcerol 3-phosphates pathway associated with smooth endoplasmic reticulum and rough endoplasmic reticulum and then, resynthesised CM are transported to golgi, exocytosed

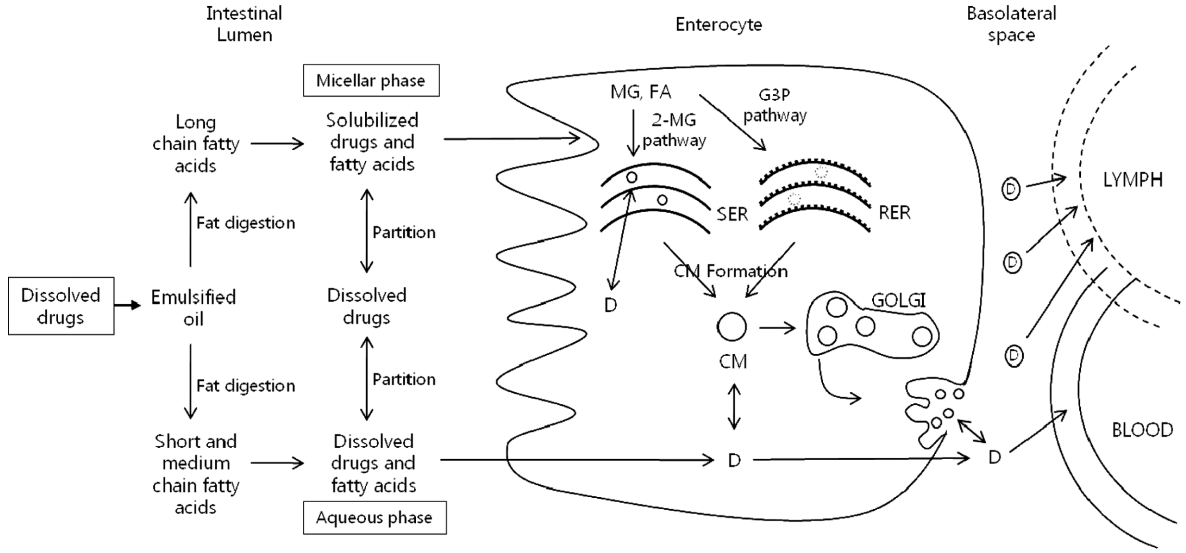

Figure 2. Illustrated mechanism of intestinal lymphatic absorption. Absorbed MG and FA are resynthesised to CM by 2-MG pathway and G3P pathway associated with SER and RER. Drug molecules combine with CM during/after CM formation. CM are then transported to the golgi, exocytosed from the enterocyte and taken up into lymphatics. D, drugs; Ⓓ, drugs associated with chylomicron; MG, monoglycerides; FA, fatty acids; 2-MG, 2-monoglycerides; G3P, glycerol 3-phosphates; SER, smooth endoplasmic reticulum; RER, rough endoplasmic reticulum; CM, chylomicrons.

from the enterocyte to basolateral space. The liphophilic drugs are associated with liphophilic core at CM assembling stage and with assembled CM in enterocyte and intercellular space. The drugs associated with CM cannot enter the portal blood and they are absorbed to lymphatic system (Fig. 2). So, the association of lipophilic drug with CM is a critical and determining step to ascertain intestinal lymphatic absorption of lipophilic compound. Indeed, Gershkovich and Hoffman demonstrated a strong linear correlation between the degree of uptake of compounds by isolated chylomicrons and intestinal lymphatic transport (Trevaskis et al., 2008; Gershkovich and Hoffman, 2005).

On the other hand, making lipid based formulation, size of carriers and kind of lipids contribute to the extent of lymphatic uptake. When materials are absorbed across the small intestinal epithelial cells, the materials with small size enough to penetrate blood capillaries show low intestinal lymph delivery ability. The reason is that the rate of fluid flow in the portal blood is approximately 500 fold higher than that of the intestinal lymph (Melody A et al., 2001). However, the absorption of macromolecules or colloids to have higher molecular weight relatively tends to selective transport into lymphatics since lymphatics endothelium is more permeable than blood capillaries endothelium. Because lipid formulations are not thought to be absorbed intact in rough condition of the digestion process, in fact, carrier size may seem less important.

Influence of lipids kind for formulation about the extent of drug lymphatic delivery also has been extensively reviewed (Trevaskis et al., 2006; O'Driscoll, 2002; Nankervis et al., 1996). The extent of lymphatic absorption across the enterocytes is the minority. Otherwise, the primary process for lymphatic uptake is composed of a cascade of consecutive events that includes uptake of the drug into the enterocyte, and association of drug with lipoproteins (Trevaskis et al., 2008; O'Driscoll, 2002). For enhancing intestinal lymphatic delivery, fatty acid used to consist of lipoprotein must have 14 chain length or greater. As lipid chain length is longer, lipoprotein is more hydrophobic. So, lipoproteins are more transported to lymphatics. In addition, mono- and poly- unsaturated fatty acid promote lymphatic uptake of lipoprotein. Because unsaturated fatty acids produce larger sized lipoproteins compared with the equivalent saturated fatty acid (Nankervis et al., 1996; Charman and Stella, 1986).

According to recently study carried out by Trevaskis et el (2006), the intestinal lymphatic delivery of lipophilic drugs is greatly affected by lymph lipid precursor pool (LLPP) located in the smooth endoplasmic reticulum and golgi, and comprised primarily of lipids derived from exogenous sources. The result said that the extent of intestinal lymphatic delivery of lipophilic drugs was dependent on the size of LLPP and the source of lipids composing LLPP. Although the extent of lymphatic uptake seems to rely on the size of LLPP, most crucial factor is the source of lipids. Exogenous and biliary derived endogenous lipids in LLPP encourage lymphatic delivery of lipids and drugs, otherwise endogenous lipids from basolateral side cannot do that. In addition, L-α-lysophosphatidylcholine (LPC)

added to experimental formulations expanded the size of LLPP and increased the mass of biliary lipid secretion, as a result it showed the improvement of lymphatic delivery (Trevaskis et al., 2006). It suggests that formulation components such as LPC, which can expand the LLPP and stimulate biliary lipid secretion, may enhance lymphatic drug transport and it reconfirms that the composition of formulation is important factor of lipid-based carrier to target to intestinal lymphatic system.

In short, lipid-based carrier is considered a suitable candidate for intestinal lymphatic delivery due to the nature of intestinal lymphatic system, and the crucial factors determining the efficiency of lymphatic delivery are the kind and the quantity of carrier components.

Nanocarriers for Lymphatic Delivery

Polymer based carrier

Biodegradable polymers have been extensively studied to enhance the targeting ability to the lymphatic systems, to increase bioavailability by preventing enzymatic degradation and to improve the drug loading and/or the physicochemical stability of other colloidal carriers (Y. Nishioka et al., 2001). Natural polymer such as dextran and hyaluronic acid, as well as synthetic polymers such as poly(lactide-co-glycolide) (PLGA), poly(L-lactic acid) (PLA), and polyhexylcyanoacrylate (PHCA) have been most extensively investigated as drug carriers for targeted lymphatic delivery (Rao et al., 2010; Xie et al., 2009).

Nano carrier system based on polymers is structurally classified to nanocapsule, nanosphere, nanotube, and dendrimer. Nanocapsule and nanosphere are mainly studied among them for lymphatic delivery. Nanocapsule is vesicular system in which the drugs are confined to a core surrounded by a polymer membrane, whereas nanosphere is matrix system in which the drugs are dispersed. Lymph targeting mechanism of these systems comes from two natures of polymeric nanocarrier that are nanometer size and biodegradable. Due to small size of carrier, carriers can be delivered to lymphatics. Delivered carriers function as reservoirs in lymphatics and show the specific drug release patterns depended on polymers making up of the carriers. Lymph targeting by plan nanoparticle can be passively achieved, thus various methods for active targeting have been tried such as surface engineering and magnetic carrier (Singh and Lillard, 2009).

In our previous study, preparation and evaluation of tacrolimus-loaded nanopaticles, we could obtain PLGA and PEG: PLGA nanoparticle whose size and encapsulation efficiency were 218 ± 51, 220 ± 33 nm and 60.0 ± 1.2, 60.3 ± 2.0%, respectively. The prepared nanoparticles and the commercial product of tarcrolimus (Prograf® inj.) were intravenously administered to rats, respectively, to compare pharmacokinetic characteristics and lymphatic targeting efficiency calculated as ratio of tacrolimus concentration in lymph node to whole blood at 1 hr after administration. Pharmacokinetic parameters like AUC, CL_t, and MRT were significantly different compared with those of Prograf®. Both prepared nanoparticles showed 2~3 fold higher the concentrations of tacrolimus in mesenteric and axillary lymph nodes after i.v. administration than those of Prograf®. Also, lymphatic delivery efficiency was enhanced, too (Shin et al., 2010).

Liposome

Liposomes are nano size vesicles composed of amphiphilic monomers that form a bilayered membrane, with the monomers arranging within the membrane so that the hydrophilic ends point towards hydrated surface. These are great scientific and medical interests due to their ability to protect, encapsulate both hydrophobic and hydrophilic drug, and deliver selected organs (Xie et al., 2009; Allen and Moase, 1996).

Liposome can be administered via intra-muscular, subcutaneous, intra-peritoneal injection, and oral administration. Specially, extravascular injection is the most extensively investigated administration route for regional lymphatic delivery.

Conventional liposomes are taken up lymphatic by hydrostatic pressure gradient caused by the link which connects lymphatics and ECM. Therefore, the lymphatic uptake of conventional liposome is passive process. Also, these liposomes have limitations about the rapid uptake of drugs by mononuclear phagocyte system, degradation of lipids, and leakage of drugs. To overcome these limitations, the surface modification of liposome has received much attention to improve lymphatic uptake and lymph node localization of liposomes. Among the various polymers to have been investigated, poly(ethylene glycol) has been widely used as polymeric steric stabilizer (Oussoren and Storm, 2001). PEG coated liposome has many useful properties, such as lowering toxicity, increasing half-life, and decreasing clearance and immunogenicity. Despite of these advantages, PEG coated liposome is still taken up to lymphatics by passive process and the evidence suggests that some caution is needed to multiple dose, which can significantly alter the pharmacokinetic behavior of a second dose when this second dose is administered after an interval of several days. This phenomenon, called “accelerated blood clearance” (Singh and Lillard, 2009; Immordino et al., 2006).

To deliver to lymphatics by active process, liposomes con-

Table I. *Various Carriers and Drugs for Lymphatic Delivery*

Drug	Carrier[a)]	Administration route	Kind of targeting[b)]	Reference
Adriamycin	liposome	i.p.	active	Parker et al., 1981
Cefotaxime	liposome	p.o.,	active	Ling et al., 2006
Diethylcarbamazine	NP/o emulsion	s.c.	active	Karajgi and Vyas, 1994
	w/o emulsion	s.c.	active	
Methotrexate	liposome	i.m.	active	Kim and Han, 1995
	emulsion-C	p.o.	not available	Paliwal et al., 2009
	emulsion-D	p.o.	not available	
	emulsion-E	p.o.	not available	
Tacrolimus	PLGA NP	i.v.	passive	Shin et al., 2010
	PEG-PLGA NP	i.v.	passive	
Zidovudine	liposome	s.c.	passive	Kaur et al., 2008
	SA liposome	s.c.	passive	
	PCP liposome	s.c.	passive	
	Man liposome	s.c.	active	

[a)]NP, nanoparticle; SA, stearylamine; PCP, dicetyl phosphate; Man, mannose; PLGA, poly(lactide-co-glycolide); PEG, poly(ethylene glycol).
[b)]The kind of targeting is calculated as the ratio of drug concentration in lymph to whole blood or plasma. Active means that the ratio is greater than 1, otherwise passive means the opposite of that.

jugated to specific ligand that can interaction with receptor in the lymphatic vessel and macrophage resident in the regional lymph nodes are developed like polysaccharide or antibody conjugated liposomes (Feng et al., 2010).

Lipid based carrier

Mentioned above, although the uptake mechanism of lipophilic drugs isn't defined fully, several studies have claimed that lipid-based carriers such as emulsion, lipid solution, and micelle enhance the uptake to intestinal lymphatic system.

The extent of lymphatic uptake of lipophilic drugs is depended on digestibility of the carrier, nature of the fatty acid in the carrier, and dispersed state of the carrier. In general, if the fatty acids making up of carrier have long chain and unsaturated bonds, the drugs are more delivered to lymphatics due to the increased ability to stimulate chylomicron production (O'Driscoll, 2002). However, these carriers associate with many problems, including the large volumes required, poor physical stability, and complexity of manufacturing.

To overcome these problems, self-emulsifying drug delivery systems (SEDDS) have been received attentions. SEDDS are isotropic mixture of drug, lipids, and surfactants. Upon mild agitation followed by dilution with aqueous media, such as GI fluids, these systems can quickly form fine oil-in-water emulsion or microemulsion with a droplet size of less than 50 nm. Although the mechanism of self-emulsification is not yet well understood, it was considered that self-emulsification occurs when the entropy change favoring dispersion is greater than the energy required to increase the surface area of the dispersion. The delivery using SEDDS can minimize the burst of emulsion, enhance the dissolution and permeability of drugs due to small size and well-proportioned distribution, protect drugs against hydrolysis by enzymes in the GI tract, and reduce the presystemic clearance in the GI mucosa and hepatic first-pass metabolism. The extent of lymphatic uptake is altered as the kind and quantity of lipids, surfactants, and solvents consisting of SEDDS. Specially, the amount of surfactants is important cause of toxicity. To achieve enhanced lymphatic targeting, it is needed to maximize drug loading while minimize surfactant and solvent concentrations. Although SEDDS have not been exploited for lymphatic delivery, it may have potential as lymphatic delivery system in near future (Kohli et al., 2010; Gursoy and Benita, 2004).

In summary, SEDDS comprised of appropriate lipids and co-components is thought as most promising method for enhancing the lymphatic delivery efficiency of carriers administered via oral route and this will be able to be actively targeted to lymphatic system by chemical modification of vehicle components with active moiety. Even if polymer-based nanocarrier, liposome, and lipid-based vehicle can be utilized for intestinal lymphatic delivery system, lipid-based vehicle is regarded as suitable intestinal lymphatic delivery carriers with respect to manufacturing processes, physiochemical stability and pharmacokinetic features. However, it still has the lim-

itation which is the lack of ability for active lymphatic targeting.

Conclusion

As the physiological and pathological functions of lymphatic system have been identified, the importance and necessity of lymphatic drug delivery system are highlighted. Due to the anatomical feature of lymphatics, numerous studies using carriers for lymphatic delivery have been mainly researched.

In summary, the lymph targeting drug delivery systems have utilized the polymeric nanoparticle, liposome, and lipid-based vehicle as drug carrier whose extent of lymphatic uptake is determined by several factors such as carrier size, composition, hydrophobicity and surface character. When carriers are administered via parenteral routes, the most crucial factor is carrier size since the feature of lymphatic capillary, and the lymphatic delivery ability of carriers are enhanced by attaching of specific ligand interacting to substance in lymphatic system, coating by polymers, and modulation of composition for adjusting of hydrophilic property. Otherwise, because carriers administered to oral route are rarely absorbed through enterocyte directly, carrier size for oral route is thought less important compared to carrier composition affecting to synthesis of chylomicrons.

Although lymphatic targeting using carriers indicated clearly high lymphatic delivery efficiency compared with that of conventional dosage forms, it didn't show whole lymph selectivity. If we can develop the methods of active lymphatic targeting, establish a convincing theory about factors determining the lymphatic uptake of carriers, and suggest the pharmacokinetic model which can predict the behavior of drugs in lymphatic system, we may optimize chemotherapy to maintain ideal concentration of drugs in lymphatics.

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