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Review Article

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Lymphatic system and Nanoparticulate carriers for lymphatic delivery

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Abstract

The lymphatic system consists of lymph, lymphatic pathways such as lymphatic capillary, lymphatic vessel, lymphatic duct etc., and some lymphatic organs including lymph node, thymus, and spleen. The delivery of drugs and bioactive compounds via the lymphatic system is dependent on the physiology of the system. The lymphatic system is able to avoid first-pass metabolism, thus the lymphatic system is suitable for compounds with lower bioavailability, i.e., those undergoing more hepatic metabolism. The lymphatic route also provides an option for the delivery of drugs to treat cancer and human immunodeficiency virus, which can travel through the lymphatic system. The lymphatic route plays an important role in transporting extracellular fluid to maintain homeostasis and in transferring immune cells to injury sites. This paper provides a detailed review of novel lipid-based nanoformulations and their lymphatic delivery. The uptake and distribution of lipid-based nanoformulations by the lymphatic system depends on factors such as particle size, surface charge, molecular weight, and hydrophobicity. Nanoparticulate carriers and their lymphatic delivery via different routes, as well as the in vivo and in vitro models used to study drug transport in the lymphatic systems are also discussed.

Keywords: Lymphatic system, Nanoparticulate carriers, Liposomes, Lymphatic capillary.

1. Introduction

The lymphatic system consists of lymph, lymphatic pathways, such as lymphatic capillary, lymphatic vessel, lymphatic duct etc., and some lymphatic organs including lymph node, thymus, and spleen. The major function of the lymphatic system is to maintain the body's water balance to the normal level as blood vessels do [1, 2]. This system plays an important role in helping to defend the tissues against infection by filtering particles from the lymph and by supporting the activities of the lymphocytes, which furnish immunity, or resistance, to the specific disease causing agents. Also, it is well known that the lymphatic absorption of a drug after intestinal administration provides an advantage over the portal blood route for the possible avoidance of liver pre-systemic metabolism (hepatic first-pass effect). Due to such fundamental functions or characteristics, many attempts have been made to utilize the lymphatic system for the route of drug delivery, which have been reviewed by Muranish [3]. The lymphatic system differs from the vascular system in capillary structure, circulation pattern, and functions. The lymphatic route

is known to be one of the primary pathways for tumor metastasis. Tumor cells that have detached from the tissue or have invaded a lymphatic vessel become trapped in the meshwork of a lymph node. Some metastatic cancers appear to spread almost exclusively via lymphatics, whereas others also spread through the vascular system [4]. Research into lymphatic targeting has recently attracted increasing interest not only for providing a preferential anticancer chemotherapy, but for improving oral absorption of macromolecule drugs, or achieving mucosal immunity. The lymphatic system is the site of many diseases such as metastitial tuberculosis, cancer, and filariasis [5]. The lymphatics, especially lymph nodes, are also one of the secondary lymphoid organs as is the spleen, Peyer's patches and appendix, and as are the sites where immune responses are initiated [6,7]. thymus-dependent small lymphocytes, large lymphocytes and macrophages present in lymph nodes produce circulation antibodies, and are involved in immunological reactions.The functions of the lymphatics depend on the blood-lymph communications in various tissues and organs. The large molecular complexes and particles that enter the tissue-fluid will generally be taken up by the fine network of lymphatic capillaries. The lymph passes through one or more lymph nodes and is further transported, via efferent vessels, to the great vein at the base of the neck. While blood circulation generally goes to and returns from every tissue via arteries and veins, lymph flow is usually one-way transport which starts from each tissue and is directed towards the central regions such as the thoracic duct (8).

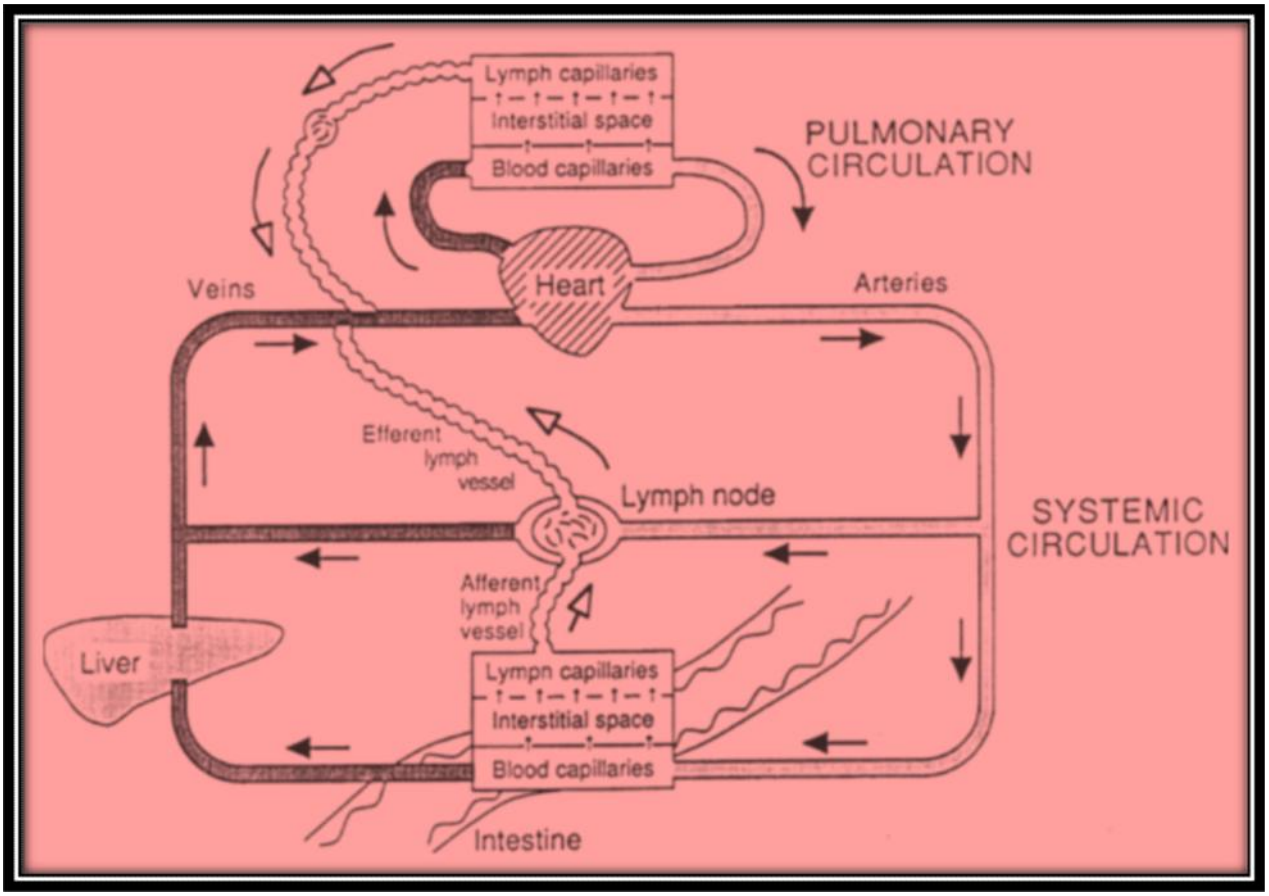

Fig. Lymph- blood communication in body.

2. Effects of carrier systems and administration

A number of water-soluble molecules with a molecular weight of less than 5000 are distributed in equal concentrations between blood and lymph where they do not bind to any endogenous proteins or microparticles: in other words, the concentrations of smaller molecules do not specifically increase in lymph compared to that in blood fluid. Firstly, if peptide drugs are not large enough, carrier systems such as microparticles or soluble macromolecules of appropriate sizes should be chosen for lympho-selective delivery [8]. Physical complexed binding, incorporation or chemical conjugation to the carrier

system may be applied depending on the properties of the peptide drugs. Secondly, since numerous peptide-degradation enzymes, such as amino-peptidases and endopeptidases, are present in various organs and tissues, strategies for protecting against peptide degradation by various enzymes are usually required [9,10]. Carrier systems may often overcome these obstacles: they can increase the residence time of peptides in the lymph circulation, or can enhance the bioavailability of peptides in the are where they are needed [11,12]. Gn the other hand, the sites of drug administration considerably influence the lymphatic transport of drugs. For examples, when macromolecules such as dextrans are injected intravenously, an increase in molecular size will decrease the permeability across the blood capillary, and result in a lymphlplasma (LIP) ratio of less than 1 [13,14,15,16]. Under normal tissue conditions, a sufficiently high LIP ratio cannot usually be obtained by intravenous administration. When the small molecules are injected interstitially, about equal concentrations between blood and lymph will be obtained, resulting in a LIP ratio of 1 [17,18,19,20]. Microparticles injected into tissues such as the stomach wall and subcutaneous areas are mainly delivered to lymphatics, resulting in LIP ratios larger than 1[21,22,23,24]. The reason why the lymph levels become higher than the blood level is that large molecules penetrate through intracellular gaps of the lymph capillaries despite toe difficulty in blood capillary penetration [25,26,27,28,29]. When the macromolecules are administered into a lumen such as the intestine and lung, they have to pass through the mucosal epithelium prior to reaching lymph and blood vessels. The penetration of mqcromolecules is often tricky: it is difficult for them to pass through the epithelial cells, but for example, pinocytotic uptake in Peyer's patches or penetration through large pores in the alveolar membrane occurs depending on their routes of entry into the body [30,31,32,33,34]. If they can penetrate these barriers, lymphatic uptake of macromolecules or particles would be easily achieved. The gastrointestinal tract is certainly one of the routes for peptide administration [35,36,37]. First, transfer into lymph vessels via absorptive epithelial cells (villous) occurs in two ways: one is the transcellular lipid pathway in which chylomicrons are formed in the cells and transferred into lymph capillaries (Fig. 2a), and the other is the paracellular pathway which usually contributes little, but operates by the addition of absorption enhancers (Fig. 2b) [38,39,40]. The second route is transcytosis through Peyer's patches, and this seems to be most suited for highly potent compounds such as lymphokines and vaccines (Fig. 2c) [41,42].

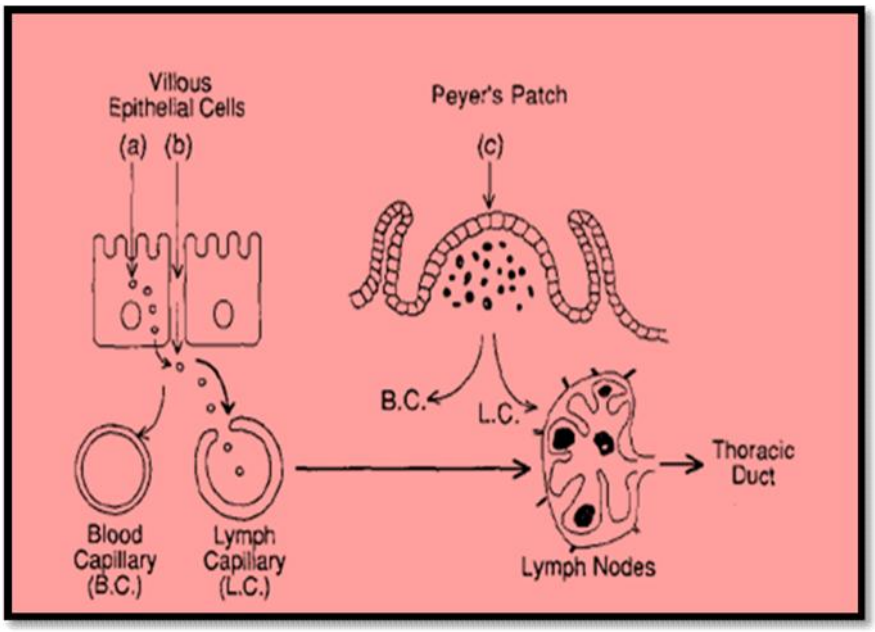

Fig. Lymphatic transfer of drugs via small intestinal epithelial cells and Peyer's patches.

3. Drug –Carriers and drug for lymph targeting[8].

Table-1

Lymphotrophic carrier	Drug
Carbon colloid	Mitomycinc, aclarubicin
Dextron	Mitomycinc, Adriamycin
L-Lactic acid oligomer microsphere	Aclarubicin, cisplatin
Gelatin microsphere	Mitocin c
β-Cyclodextrin oligomer	1-Hexyl-5-fluorouracil
Intrinsic protein complex	Vitamin B12
Styrene-maleic acid anhydride co-plymer	Neocarzinostatin
s/o emulsion	5-fluorouracil, bleomycin
Lipid mixed micelle	Interferon,thf
Chylomicron, LDL	Cyclosporin, vitaminA. Co-enzymeQ
Dextron sulphate	Bleomycin

4. Formulations for lymphatic targeting

Table-2

Formulations	Drugs	References
Emulsion	Penclomedine	11
Emulsion	Ontazolast	12
Microemulsion	Puerarin	13
Microemulsion	Raloxifene	14
Micellar systems	Cyclosporin A	15
SEEDS	Coenzyme Q10	16
SMEDDS	Halofantrine	17
SMEDDS	Nobiletin	18
SMEDDS	Valsartan	19
SMEDDS	Vinpocetine	20
SMEDDS	Silymarin	21
SMEDDS	Sirolimus	22
SNEDDS	Carvedilol	23
SNEDDS	Valsartan	24
SNEDDS	Halofantrine	25
Liposomes	IgG1	26
Liposomes	Doxorubicin	27–28
Liposomes	Cefotaxime	29
Liposomes	9-nitro-camptothecin	30
Liposomes	Paclitaxel	31
Liposomes	Ovalbumin	32
SLNs	Etoposide	33
SLNs	Methotrexate	34
SLNs	Idarubicin	35
SLNs	Tobramycin	36,37
SLNs	Nimodipine	38
NLCs	Testosterone	39
NLCs	Vinpocetine	40
NLCs	Tripterine	41

5. Nanoparticulate carriers for lymphatic delivery

5.1. Emulsions

Preferential lymphatic transport of mitomycin C has been demonstrated following injection of W/O or O/W emulsions via the intraperitoneal and intramuscular routes [43]. It was reported that selective uptake after injection into the regional lymphatics occurred in the order of O/W. W/O. aqueous solution. Hashida et al. [43, 44] developed gelatin spheres in oil (S/O) emulsion for minimizing the instability of the W/O emulsion. The nanoparticle-inoil emulsion system, containing anti-filarial drug in gelatin nanoparticles, were studied for enhancing lymphatic targeting [45], and it was suggested that this colloidal system holds excellent potential as a lymphotropic carrier system. More recently, an emulsion formulation consisting of an anticancer drug, Pirarubicin, and LipiodolÒ was developed to treat gastric cancer and metastatic lymph nodes [46].

5.2. Liposomes

Liposome, a nano-sized biodegradable lipid vesicle with aqueous space surrounded by a lipid bilayer, has received considerable interest as a vehicle for drug targeting to the lymphatic system. Earlier studies suggested that liposome-entrapped compounds were selectively transported into lymphatic tissue following intraperitoneal administration [47,49], intramuscular or subcutaneous injection [50,51]. The effect of liposome size was evaluated by intraperitoneal administration of liposomes with 0.72–0.048 mm in diameter and having identical compositions [48]. Liposome size significantly altered both fractions of lymphatically absorbed drug retained in lymph nodesand drug recovered in the thoracic duct lymph. The largest liposomes were those most retained by the lymph nodes. It is thought that smaller liposomes pass unretarded through the lymph nodes but that larger liposome may be predominantly entrapped by lymph node tissues during physical filtration. Lymphatic uptake of liposomes of various sizes, lipid composition, and surface characteristics were investigated [52,53]. The main factor controlling lymphatic uptake after subcutaneous administration appeared to be liposome size, and small liposomes seemed to be preferred to achieve high lymphatic uptake. The surface charge of liposomes and the route of administration were reported to be important for the lymphatic delivery of drugs [54]. Following lymphatic uptake, liposomes pass through a system of lymphatic vessels and encounter one or more lymph nodes, where a fraction will be retained. It has been suggested that phagocytosis by macrophages is one of the major mechanisms of uptake of colloidal particles in lymph nodes [55,56]. Reduced lymph node localization of liposomes in macrophage-depleted lymph nodes confirmed that phagocytosis by macrophages plays an important role in lymph node retention of liposomes [57]. To enhance targeting ability, various attempts have been made so far, including immunoliposome [58], PEGylated liposome [59], and galactosylated liposome [60]. One example of clinical application is the endoscopic gastric submucosal injection of liposomal adriamycin, which provided an enhanced lymph node targeting delivery to considerably higher levels than intravenous free adriamycin in patients with gastric cancer [61–63]. As another example, a pilot study of liposomal mitoxantron for breast cancer was reported [64]. Lymphatic targeting is thought useful for diagnostic purposes. A case study is reported using blue violet entrapped in liposomes to localize lymph nodes before surgery [65].Polymerized liposomes were developed by Langer et al. [66]. The liposomal structure highly stabilized by cross-linking of lipid bilayer allows the oral administration of those carriers to achieve more efficient uptake from Peyer's patch [67].

5.3. Nanoparticles

Biodegradable, polymeric nanoparticulate systems have been developed to enhance the targeting ability to the lymphatic systems or to improve the drug loading and/or the physicochemical stability of other colloidal carriers. A wide range of studies on the preparation of polyalkylcyanoacrylate nanoparticles and their therapeutic applications has been conducted

by the research groups of Puisieux and Couvreur [68,69]. The lymph targeting of polyhexylcyanoacrylate nanoparticles was evaluated after intraperitoneal administration in rats. It was found that these particles were of potential use in treating tumors that metastasize in the peritoneal cavity or via lymphatic pathways [70,71]. They showed that uptake via Peyer's patches or isolated lymphoid follicles of insulin-loaded polyisobutylcyanoacrylate nanocapsule occurred after oral administration, suggesting the possibility of peroral peptide delivery [72]. Davis and Illum have conducted extensive investigations on biodegradable nanospheres with polylactides and poly(lactide-co-glycolide) as carriers for achieving the efficient delivery of drugs and diagnostic agents to the lymphatic system. To enhance lymphatic drainage and

lymphatic node uptake of nanospheres, various methods of surface engineering have been tried, including surface coating with poloxamines or poloxamers [73] and the use of polyethyleneglycols [74]. Besides the drug delivery purpose, Magnetite-Dextran nanoparticles have been investigated for diagnostic use and found potentially useful as contrast agents in magnetic resonance imaging (MRI) [75]. Lipid-based nanospheres should be alternative colloidal carrier systems for lymphatic targeting. The solid lipid nanoparticles (SLN) were developed and evaluated for the lymphatic uptake after intraduodenal administration to rats [76,77]. A liposomal mimetic formulation, a phospholipid dispersion containing dipalmitoyl-phosphatidylcholine (DPPC) and Emulphor, was also developed and found to achieve higher lymphatic uptake of drug compared to conventional DPPC liposomes [78,79]. As other nano-sized drug carriers, activated charcoal particles have been extensively studied for diagnostic
purposes and the targeted delivery of anticancer drugs to the regional lymph node [80–82].

6. Models for study of drug transport in the lymphatic system

6.1. In vivo models

In this model cannulation of the mesenteric or thoracic lymphatic ducts is performed in animals to investigate drug transport in the intestinal lymphatic system[83].in this model drug concentration are directly measurement of in lymph. The procedure cannot be performed on humans because it is an irreversible and invasive surgical process [84]. In this model Small animals like rats, are commonly used, but some larger animals, including sheep, rabbits, dogs and pigs, have also been used[84-92].

Another in vivo model is the lymphatic venous shunt, in which drug concentrations in lymph are measured at fixed time intervals, and lymph is collected over a longer period of time. Further, an indirect method has been used in an oral bioavailability study to evaluate intestinal lymphatic drug transport in both the presence and absence of inhibitors of intestinal chylomicron flow. This method has the advantage of not requiring a surgical procedure, as does the lymphatic duct cannulation model [93–96].

6.2. In vitro models

Various in vitro models can serve as an alternative to in vivo models for studying lymphatic drug transport. In the intestinal permeability model, Caco-2 cells are used to evaluate intracellular lipoprotein-lipid assembly and to examine the effect of lipids and lipidic excipients on incorporation of drug with lipoproteins in lymphatic transport [97–99]. In one in vitro model, Gershkovich and Hoffman described a correlation between the degree of ex vivo incorporation of a drug into chylomicrons and the extent of intestinal lymphatic drug transport [100]. According to a lipolysis model described by Dahan and Hoffman, in vivo drug absorption could be predicted by evaluating drug release from a lipid-based drug delivery system and estimating precipitation of the drug during lipolysis [101]. Holm and Hoest reported an in silico method that established a quantitative relationship between the molecular structure and amount of drug transferred from the intestinal to the lymphatic system [94–96,102].

7. Conclusion

In current scenario liposomes and solid lipid nanoparticles emerges as a new technology to provide better penetration into the lymphatics where residual disease exists. the lymphatic route can be used for delivery of cytotoxic agents and therapeutic molecules with higher first-pass metabolism and lower solubility so method can serve as a bypass route, especially for anticancer and anti-human immunodeficiency virus drugs, both of which target diseases utilizing the lymphatic system. Drugs that are encapsulated in lipid-based nanoformulations, such as NLCs, are better candidates for lymphatic drug delivery.

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