Lymphatic transport of orally administered drugs

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Several therapeutic molecules such as lipophilic drugs and peptides suffer from the problems of low oral bioavailability. Improvement of their bioavailability and simultaneous prevention of the oral degradation of the prone molecules appears to be a challenge. Lymphatic system, which is responsible for the maintenance of fluid balance, immunity and metastatic spread of cancers, is also found to play a major role in the oral absorption of lipids and lipophilic drugs from intestine. The specialized structure of gut associated lymphoid tissue can be utilized as a gateway for the delivery of particulate systems containing drugs. Even though a large gap has existed in the field of lymphatic drug delivery, the introduction of a large number of lipophilic drugs and peptides has brought a renewed interest of research in this area. In this review, the mechanisms of intestinal lymphatic drug transport, approaches taken for the delivery of macromolecules, lipophilic and peptide drugs, biochemical barriers involved in intestinal drug absorption, and animal models used in the studies of intestinal lymphatic drug transport have been discussed.

The drug uptake and transport into the body through intestinal lymphatics has recently received considerable attention. The specialized structure and functions of the lymphatic system allows the site-specific delivery to lymph and lymphoid tissue (B- and T-lymphocytes), of cytokines and immunomodulators and in the treatment of viral diseases like AIDS, the sites associated with low density lipoprotein receptors and delivery to systemic circulation. The intestinal lymphatic drug transport prevents the first-pass metabolism of several prone drugs and improve the oral bioavailability of highly lipophilic drugs. Physiologically, a majority of the orally administered drugs diffuse into the enterocytes and get absorbed into the portal vein and after processed in the liver, enter the systemic circulation. But, the highly lipophilic moieties may gain access to the intestinal lymphatics and enter the systemic circulation via the thoracic lymph duct. The process time of the lymphatic absorption and transport is slower than that of the portal blood, because of a sequence of complex events involved in the lymphatic transport, and hence the plasma profiles of drug absorption by both processes vary.

The orally administered lipids are digested and absorbed into the intestinal lymphatics, and the particulate systems may gain access to the intestinal lymph through the gut associated lymphoid tissue (GALT).

Several therapeutic substances like macromolecules including peptides and peptidomimetics, highly lipophilic drugs and their prodrugs have been attempted for intestinal lymphatic delivery, and their physicochemical requirements for better lymphatic absorption have been studied. Delivery systems containing lipids and biodegradable polymers have been developed, and the effect of various lipids and polymers in the lymphatic transport has been described. In this review, the aspects regarding anatomy and physiology of the lymphatic system, mechanisms of drug access to lymphatics from intestine, various attempts done to enhance the intestinal lymphatic drug absorption and animal models used in the assessment of lymphatic drug concentrations have been discussed.

Physiological anatomy and functions of the lymphatic system

The lymphatic system consists of lymph ducts, lymph nodes and lymphoid tissues distributed in all areas of the vascular tissues of the body, which function to absorb the excess fluid and cellular elements like proteins and lipids, not reabsorbed by the blood capillaries. The lymphatic system do not form a circular system like blood vascular system, and has a unidirectional flow of lymph, collecting lymph from peripheral tissues and emptying into the vascular system. The terminal lymphatic capillaries in the periphery collect lymph and unite to form collecting (afferent) lymph ducts that transport lymph to the regional lymph nodes. Post nodal (efferent) lymph ducts
drain the lymph between successive sets of lymph nodes and ducts into the collecting reservoir known as cysterna chyli, which also receive lymph from the intestinal, hepatic and lumbar regions. Ascending part of the cysterna chyli is continued into thoracic lymph duct (major lymphatic vessel), collecting lymph also from mediastinum and cranial parts of the body except the right quadrant and empties into the venous circulation at the junction between left internal jugular and left subclavian vein. Lymph from the upper right quadrant of the body may drain into the right thoracic lymph duct that empties into the venous circulation at the junction of the right internal jugular and right subclavian vein.

Lymph is derived from intestinal fluid and contains most of the components of the plasma, but in lower concentrations proportion of other components being less important. The lymph enters the lymph nodes by afferent lymphatic ducts and flows through medullary sinuses lined with macrophages that are responsible for phagocytosis of cellular and particulate matter, and exits through hilus into an afferent lymphatic. The mechanisms of exchange of various materials between blood and lymph are poorly understood.

The lymphatic capillaries of small intestine (lacteals) are located in the central part of each intestinal villi, and are bigger in size than that of the lacteals of the large intestine. These capillaries from both small and large intestine unite with capillaries of mucosa and submucosa and form larger collecting lymphatics. The collecting lymphatics from small intestine and the ascending and transverse colon unite to form the superior mesenteric duct, which runs into the cysterna chyli, and through thoracic duct, opens into the vascular system. The permeability of lymphatic capillaries to large molecules is more than that of blood capillaries. The fluid flow rate of portal blood is around 500 times greater than that through lymph and hence, most of the orally administered drugs are preferentially absorbed into the portal circulation. Nevertheless, the specialized structure of the lymphatic capillaries may allow macromolecules and colloids for the lymphatic transport.

**Mechanisms of drug access to lymphatics from intestine**

The drug access to intestinal lymphatics can be explained by three mechanisms.

1. **Macromolecular compounds** are often favoured for intestinal lymphatic transport because of high molecular size. Small polar molecules could also be converted into macromolecular conjugates or their prodrugs can be prepared, for improved intestinal lymphatic transport.

2. **Lipid digestion and absorption pathway** in the intestine, could form an important route of the intestinal lymphatic absorption and transport of highly lipophilic drugs with high pKa values. The drugs incorporated into the lipids, associate with them all throughout their digestion and absorption process, and transported to the lymphatic system.

3. **Drugs incorporated into the colloidal systems**, undergo intestinal uptake by the lymphoid follicles and Peyer’s patches (PP) of the GALT, and transported to lymph directly or by phagocytosis effect of macrophages.

**Lymphatic transport of macromolecules from intestine**

The higher molecular size of macromolecules, avoids their absorption into the portal circulation and promotes uptake by intestinal lymphatics. Intestinal lymphatic transport of several macromolecules like enteric endotoxin, enterostaphylococcal endotoxin, clostridium botulinum toxin, horse radish peroxidase, albumin and elastase has been reported. However, the extent of macromolecular absorption is very limited, and is restricted by the barrier function of the intestine. The improvement of intestinal absorption of macromolecules could be achieved by the use of penetration enhancers. Yoshikawa et al. studied the effect of penetration enhancer on lymphatic transport of fluorescent labeled dextrans. These dextrans having molecular weights 10, 20, 40 and 70kD were dissolved in penetration enhancer and administered to small and large intestine. From both the small and large intestine, the comparatively high molecular weight dextrans (HMD) (40 and 70kD) showed good affinity to intestinal lymphatics than that of the other dextrans in the study, which may be due to the decreased permeability of blood capillaries to HMD.

Mixed micellar systems (MMS) have also been utilized for the absorption enhancement studies of α- and β-interferon from the large intestine. MMS containing human fibroblast β-interferon also showed more affinity to intestinal lymphatics resulting in very low blood concentration. Nevertheless, the penetration enhancers should be used with caution, because of their toxicity related problems.
Lymphatic transport of lipophilic molecules from intestine through lipid absorption pathway

Highly lipophilic drugs could be delivered to intestinal lymphatics by association with dietary lipids. The dietary lipids are digested in the intestine, absorbed into the intestinal lymphatics and transported to the systemic circulation. In this case, the absorption of drugs does not depend on their molecular size, but it is the extent of lipophilicity and chain length of lipids that determine the drug absorption. Better drug candidates for this route of absorption would be the molecules having high pKa value indicating high lipophilicity and good lipid solubility, which allows better association with lipoproteins formed during the re-esterification of triglycerides in the enterocyte. The digestion and absorption pathway of dietary lipids is shown in Fig. 1.

Digestion and absorption of dietary lipids

The normal diet contains lipids predominantly in the form of triglycerides (TGs). These TGs undergo hydrolysis by the action of lingual and gastric lipases, resulting in the formation of diglyceride (DG) and fatty acid (FA) in the stomach. The shear produced by the antral contractions aid in the formation of crude emulsion of the above amphiphilic lipid digestion products (LDPs) and their emptying into the duodenum. Lipid entry into the duodenum stimulates the release of pancreatic fluids, and bile salts and biliary lipids from gall bladder, which aid in the formation of a more stable emulsion having high surface area. The action of pancreatic lipase and co-lipase on the surface of emulsion droplets, result in the formation of one molecule of 2-monoglyceride (MG) and two fatty acid molecules (FA) for each molecule of TG. These LDPs pinch off from the surface of emulsion and form liquid crystalline structures, which in the presence of bile salts form both unilamellar and multilamellar vesicles. At sufficient bile salt concentrations, these vehicles are solubilised to form mixed micelles, which greatly enhance the luminal solubility of LDPs (1000-fold) and provide a concentration gradient for the diffusion of LDPs into the enterocyte, after dissociation from mixed micelles, due to a low pH environment at the intestinal absorption site.

FAs are transported to the enterocyte by fatty acid binding protein (FABP) and fatty acid transporter (FAT). Finally, the transport of lipids from enterocyte depends upon their chain length. Short and medium chain lipids (less than 12-C atoms) directly gain access to the portal circulation, where as the long chain lipids (greater than 12-C atoms), enter the endoplasmic reticulum (ER) and undergo re-esterification to triglycerides by one of the two pathways, i.e. monoacyl glycerol pathway (major) and phosphatidic pathway (minor). The re-esterified TG assemble into the intestinal lipoproteins, gets stabilized and fuse with basolateral cell membrane of enterocyte and transported to the systemic circulation via thoracic lymph duct.

Formulation approaches for intestinal lymphatic transport of lipophilic drugs

The important pre-requisites of drug candidates for intestinal lymphatic delivery is to possess high log P (log partition coefficient) values above 5 (which implies about 50,000 times greater affinity for lymph lipid than the portal blood) and good solubility (greater than 50 mg/ml) in triglycerides (for better association during re-esterification in the ER of the enterocyte). Examples of lipophilic drugs that were studied for intestinal lymphatic transport include naftifine, mepitiostane, DDT, benzo(a)pyrene, probucol, cyclosporine, ontazolast, and halofantrine (Table 1).

Lipid-based vehicles are generally used for enhanced delivery of drugs to intestinal lymphatics, in a view that they stimulate the lymph lipoprotein turn over through the enterocyte, and increase the lipoprotein-based lipid sink into which the drugs can partition. Several lipid-based delivery systems of different compositions and functional properties have been attempted for the formulation of lipophilic drugs. The lymphatic transport of ontazolast, a highly lipophilic and potent LTβ4 inhibitor has been studied by administering as an aqueous-based suspension and four different lipid-based emulsion systems. The results indicate that the emulsion systems provided higher lymphatic drug concentration in comparison to aqueous suspension. In another study, similar results were observed by Hauss et al. in case of a lipophilic lipid regulating agent.

However, on the other hand, some interesting observations were made, indicating high lymphatic transport of drugs from non-lipid based (lipid-free) vehicles. In case of a 5a-reductase inhibitor, the administration of aqueous suspension formulation showed increased lymphatic transport, when compared to other lipid-based formulations. Similarly, an aqueous polysorbate 80 micellar solution containing retinyl palmitate showed a two-fold increase in...
lymphatic absorption, than the lipid-based systems. However, in some studies, not much difference was found in lymphatic transport of drugs, when lipid and non-lipid based systems were used. The enhancement of lymphatic transport of drugs from non-lipid based vehicles may be due to increased solubilization and altered membrane permeability due to surfactants.

Apart from the drug characteristics, the choice and properties of co-administered or drug-carrier lipids such as lipid class, fatty acid chain length and degree of unsaturation were also found to affect the intestinal lymphatic drug transport. Individual lipids differ in their rate of absorption and biochemical metabolism. The greater the degree of unsaturation of the fatty acid, the rapid the onset of chylomicron synthesis, and rapid transport to the mesenteric lymph. Hence, proper selection of lipids is necessary for producing a formulation with better lymphatic drug ab-

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Fig. 1 — Schematic representation of digestion and absorption pattern of dietary lipids
sorption capabilities. For further details regarding lipid selection and formulation related issues in the development of oral lipid-based delivery systems, the interested readers are referred to a recent review by Wasan.

The in vitro determination of digestion profiles and phase behavior of the lipids used in the lipid drug formulations, may be useful in predicting the fate of drug during the phase of lipid digestion. (i.e. the pre-absorptive phase). The rate and extent of digestion and phase behavior of the lipolytic products depend much on the fatty acid chain length. The extent and rate of digestion and aqueous phase distribution of medium chain lipolytic products is greater than the corresponding long chain lipids and is independent of bile salt concentration, to produce monoglyceride and fatty acid. This is due to the partial ionization of medium chain fatty acids to a greater extent than the long chain fatty acids at physiological pH resulting in the formation of sodium or calcium soaps or incorporation into bile salt micellar systems to form aqueous dispersions. The phase behavior of the dispersion systems in the intestine is important in directing the dietary lipids to the absorptive surface and their penetration across the enterocyte. Prodrug approach was also attempted for lipophilic drugs to enhance the lymphatic absorption and, increased intestinal lymph concentrations of prodrug were observed in comparison to the free drug.

Biochemical and pharmacological considerations in intestinal lymphatic drug delivery
Biochemical barriers such as enterocyte-based cytochrome P450 3A (CYP 3A) and P-glycoprotein (P-g) are one of the factors that affect the drug absorption from the intestine. CYP 3A enzymes present on the ER of the enterocyte are involved in phase I drug metabolism, and enterocyte P-g, an energy-dependent efflux transporter present in the brush border region of the intestine, limits the drug transport by retrograde efflux into the lumen. These two processes could act in an inter-relative manner in inhibiting the drug absorption. The oral bioavailability of several lipophilic drugs such as digoxin, cyclosporin, terfenadine and ritonavir is affected by one or both the above mechanisms. Studies were performed to understand the inter-relative nature of P-g and CYP 3A. Administration of cyclosporine oral formulation (Sandimmune) with and without water-soluble vitamin E (TPGS, tocopheryl polyethylene glycol 1000 succinate) in healthy volunteers, showed an increase in cyclosporine AUC in formulation containing TPGS. TPGS donot have any effect on CYP 3A metabolism, but acts as an inhibitor of P-g, which might resulted in improved drug transport through the enterocyte and hence the reduced metabolic effect by CYP 3A.

The effect of P-g efflux and the metabolism of verapamil in the intestine during its transport is studied by Johnson et al. The studies were performed in animals, by isolating the rat jejunum and mounting it in side-by-side diffusion chambers containing buffer. The drug flux and metabolism are observed in both mucosal to serosal (m to s) and serosal to mucosal (s to m) directions. The s to m flux of verapamil is found high in comparison to m to s flux, indicating the P-g efflux process, due to the reduced availability of drug to CYP 3A metabolism. Also the extent of drug metabolism was found more in the m to s direction, as a result of the prolonged residence time of the drug in enterocyte because of P-g efflux resulting in increased metabolism by CYP 3A.

In vitro cell cultures were widely used for studying the role of P-g and its inter-relationship with CYP 3A. However, a strong supportive human clinical data are still required to confirm, whether the intestinal P-g is a significant limiting barrier for drug absorption at clinically relevant doses. The membrane permeability of the drugs should also be considered while studying their susceptibility to P-g, as in some cases, the high passive permeability of drugs may compensate for P-g mediated efflux, resulting in good oral bioavailability.

The excipients used in the formulation of lipid-based dosage forms may sometimes affect the above
mentioned drug absorption limiting mechanisms, especially some surfactants and TPGS (D-α-tocopheryl polyethylene glycol 1000 succinate) are found to inhibit the P-g mediated efflux in invitro studies. Hence, consideration of all the above factors is essential in order to establish a proper correlation and utilize such interactions in modifying the drug absorption barriers and achieving improved oral bioavailability of drugs.

On the other hand, the binding of lipophilic drugs to plasma lipoproteins (chylomicrons, VLDL, LDL and HDL) was found to vary the pharmacokinetic and pharmacodynamic parameters of the drugs. Examples of drugs that bind to the plasma lipoproteins include cyclosporin, halofantrine, amphotericin and antiarrhythmic drugs. Lipoprotein binding has been shown to alter the plasma free drug concentration and hence the activity of the cyclosporin. Similar effect is observed in case of halofantrine after post-prandial administration, as a result of which, significant decrease in volume of distribution and clearance is seen. Sometimes, this interaction could also be positively utilized in site-specific delivery, wherein the drug-plasma lipoprotein bound fraction can be targeted to the lipoprotein receptors present in the body. After binding to receptors, they may undergo enzymatic degradation and release the drug, or enter the cell and facilitate drug release inside the cell.

**Lymphatic transport of drugs via gut associated lymphoid tissue (GALT)**

Drugs incorporated into the colloidal carriers such as microparticles could be delivered orally to lymphatic system via gut associated lymphoid tissue (GALT). The specialized structure of GALT facilitates the uptake of particulate systems from the intestine especially by the Peyer’s patches. The lymphoid tissue is divided into two components. GALT and gut associated lamina propria compose the central lymphoid tissue, and the lymph nodes form the peripheral lymphoid tissue. The GALT consists of lymphoid follicles (e.g., Peyer’s patches), plasma cells and lymphocytes. The Peyer’s patches play a major role in particulate uptake. Generally, the Peyer’s patches are oval in shape and are found usually on the opposite side to the mesenteric wall of the intestine. Light microscopy and electron microscopic studies showed that the Peyer’s patch is divided into four zones, a) the germinal center, b) the small lymphocytic areas, c) the inter follicular area, and d) the sub-epithelial zone.

Overlying the Peyer’s patches is the membranous epithelial cell layer known as follicle associated epithelium (FAE), which is composed of absorptive cells, goblet cells, M cells and enteroidocrine cells. FAE possess ability to transport macromolecules and also minimize their degradation during passage and along with GALT, it also performs the function of uptake of bacteria, viruses and pathogens from the intestine. M cells endocytose and transport the luminal antigens to the basolateral cell membrane, and release into the extracellular space.

The particulate systems are taken up by the Peyer’s patches and the extent of uptake depends on their size and surface characteristics. The particulate internalization studies showed that the particulate systems in the intestine, adhere to surface of the M cells, and the M cell pseudopods facilitate vesicular transfer of these particulates to the underlying lymphocytes and antigen presenting cells in the central hollow region of M cells. M cells are deficient in lysosomes, and hence the destruction of particulates is avoided during their transport through follicle associated epithelium (FAE). Majority of the particulates are taken up by the Peyer’s patches in comparison to other lymphoid follicles, and the particulate uptake across the intestine was found to be 0.01% of the dose of 170 to 250nm latex particles and only 0.0055% of the carbon particles. This was later confirmed by quantising the intestinal uptake of fluorescent microspheres through flow cytometric techniques. Though the quantity of particulate uptake is low, the rate of uptake is rapid. However, such low particulate uptake would not be advantageous for the delivery of most of the drugs, except the highly potent drugs. The findings were not similar in all the cases and some studies reported the uptake of large quantities of particulates from the intestine. In one study, the particulate uptake as high as 33% of the dose for very small particles (50nm) and less than 5% of the larger particles (1μm) has been observed. In another study, the absorption of 40% of the dose of 1.1μm and 13% of the dose of 3.1μm polystyrene particles has been reported.

As mentioned earlier, the particle size and surface properties of the particulate systems are important considerations, which also decide the extent of absorption. The extent of transport of small hydrophobic particles is more than the large and hydrophilic particles. The penetration of the particulates into Peyer’s patches is limited by their larger size, resulting in
reduced uptake, because of getting trapped in the submucosal layer of the Peyer’s patches. Reduced uptake is observed when the particulates are coated with hydrophilic polymers such as poloxamers, and increased particulate uptake, when coated with immunoglobulins (SigA) or specific antibodies (anti-M-cell antibody). These principles were also applied in the development of oral vaccines for immunization, using particulate delivery systems, as even the absorption of about 1% of the particulate systems is sufficient for antigen delivery. Hence it becomes apparent that, a careful selection of delivery vehicles is important in attempting the drug delivery via GALT. Recently, effective targeting of HIV in intestinal mucosa by 3'-Azido 3'-deoxythymidine (AZT) entrapped into poly(isohexyl cyanoacrylate) nanospheres, has been described by Oembri et al.

Intestinal lymphatic transport of peptides

Because of the large molecular size and hydrophilicity, most of the peptides suffer from the problem of low oral bioavailability, and are often degraded by proteolytic enzymes in the mucosa and various tissues. Hence, the successful oral delivery of peptides always remained a challenge to the drug delivery field. The peptides can be protected from degradation by chemical conjugation or incorporation into the colloidal carriers. A successful strategy in oral peptide delivery would be the proper selection of carrier and approaches to protect against degradation by various enzymes. Protection of some peptides from enzymatic degradation has been attempted with success (Table 2).

Administration of lipid micellar solutions containing cyclosporin A (CA), a highly lipophilic peptide with seven N-methyl groups, by intra-gastric route showed much higher levels in lymph, compared to the rectal route. The total amount of lymphatic transport of CA in rats is found to be only 2-5%. Such low concentrations, inspite of having good lipophilicity, may be due to insufficient logP (2.99 octanol-buffer) of the drug. Peptides incorporated into colloidal systems, access the lymphatic system via the Peyer’s patches in the intestinal mucosa. The particle size and surface characteristics of the carrier systems play an important role in the effective lymphatic absorption. Several peptides were attempted for oral delivery by incorporation into polymers, and a detailed review on this aspect is presented by Alle'mann et al.

Enhanced intestinal lymphatic absorption of peptides can also be achieved by administering as produgs. Yoshikawa et al. studied the intestinal absorption of bleomycin conjugated with an anionic high molecular weight dextran (500kD), incorporated in MMS, and compared with free bleomycin in MMS. In large intestine, the conjugated bleomycin in MMS showed significantly higher lymph concentrations than the unconjugated drug in MMS. However, the lymph selectivity of conjugated drug is reduced, when administered to the small intestine, which may be due to decreased stability of the conjugate in that environment. Studies on similar lines have been performed on peplomycin, which is used in the treatment of esophageal cancer.

Animal models in the assessment of intestinal lymphatic drug transport

The literature describes a number of animal models for the assessment of intestinal lymphatic drug transport. Apart from several factors affecting the lymphatic drug transport from intestine, the selection of animal models and methodologies adopted for lymph collection can have a significant influence on the data of lymphatic drug absorption and its overall bioavailability. Generally, two types of animal models such as small animal models and large animal models are used. In both of these models, depending on the advantages and disadvantages offered, at times the conscious and unconscious models were used.
Small animal models

Rat models are extensively used in the category of small animal models, because of the ease of handling and experimentation in comparison to other small animals. Both unconscious\textsuperscript{120-121} and conscious models have been used in various studies.

In unconscious rat model, the studies are performed by cannulating the mesenteric lymph duct for the collection of intestinal lymph, the carotid artery for the collection of blood and the duodenum for the administration of rehydration solution. Collection of all the lymph draining the small intestine can be ensured by mesenteric lymph duct cannulation. The absolute quantity of drug transported is calculated by multiplying the concentration in lymph by the respective lymph volume produced during the period of each collection\textsuperscript{122}. However, in order to determine the complete oral bioavailability of drug, the absorption into portal circulation is also to be considered. The unconscious rat model possess the advantage of avoidance of problems related to animal movement during experimentation, which are generally observed in conscious models. The rate of lymph flow varies with the conscious state of animal, and is 0.1-0.6ml/hr in anaesthetized animal, and may increase up to 1-3ml/hr in case of unanaesthetized animal, and such difference may be due to variation in the gastric motility, capillary permeability, interstitial fluid formation and venous return in both states in which the rate of above processes gets reduced in anaesthetised animals. In unconscious model, the effective shear caused and gastric emptying process differs and their effect on lipid digestion is largely neglected, and maintenance of animal in anaesthetised state for a long time may lead to high mortality rates.

The draw backs associated with unconscious models could be reduced by employing conscious rat models. The method used for lymph collection is similar to that of the unconscious model, except that the cannulas of mesenteric lymph duct and jugular vein are set to travel from the bottom side of the skin, and exit at the backside of the neck, and are connected to a saddle-type arrangement to allow continuous infusion and sampling. The surgical procedures involved in cannulation and sample collection are well explained by Edwards et al\textsuperscript{122}. In conclusion, the rat models are simple, easy to handle and inexpensive. Apart from the above advantages, they also possess the disadvantage that the lymphatic transport data could not be confidently extrapolated to other clinical situations, and also the administration of large dosage forms is not possible.

Large animal models

The limitations associated with the rat model could be overcome by employing the large animal models such as pig\textsuperscript{123} and dog\textsuperscript{124}, which facilitate accurate assessment of drug absorption. An anaesthetized pig model\textsuperscript{123} was developed, which allows for simultaneous sampling of lymph and blood. Before cannulation, a lipophilic dye (sudan black) is orally administered to aid in better visualization of the mesenteric lymph duct. However, the model did not found much application, because it allows only periodical sampling.

Several dog models were described for lymph collection, which involved the cannulation of thoracic duct\textsuperscript{125,126}. But in these models the need to perform thoracotomy for gaining access to the duct, complicates the process and necessitates intensive care of the animals. Rajpal et al.\textsuperscript{127} described a dog model for collection of thoracic lymph avoiding thoracotomy. More recently, Khoo et al.\textsuperscript{128} described a simpler method for direct cannulation of thoracic lymph duct to study the intestinal transport of drugs. However, in this model, the lymph cannot be collected from mesenteric lymph duct, which makes the chances of overestimation of actual intestinal lymphatic transport because the thoracic lymph duct is also supplied by peripheral sources\textsuperscript{43}. Hence, the cannulation site is also important in drug transport studies. Several other experimental factors that influence the intestinal lymphatic drug absorption studies include, fasting status of the animal, extent of rehydration and presence or absence of lipid feeding prior to surgery. Infusion of rehydration solutions and lipids were found to increase the lymph flow and extent of lymph lipoprotein transport\textsuperscript{129}.

Finally, several factors affect the accurate assessment of intestinal lymphatic drug transport. Hence a careful consideration and examination of all the aspects, starting from model selection to the methodologies of lymph collection and drug estimation is very important in proper interpretation of the data.

Conclusion

Intestinal lymphatic transport of therapeutic molecules offers several advantages like avoidance of first-pass metabolism and oral degradation associated with several peptides. The high molecular size, and the formulation related approaches taken to improve the selectivity to intestinal lymphatic transport, has led to the delivery of a large number of macromolecules. The problem of low oral bioavailability associated with a large number of highly lipophilic drugs, has
been reduced by administering into lipid-based vehicles. However, the considerations related to the lipid vehicles, and other formulation related parameters are important for the effective delivery of these drugs. On the other hand, the biochemical barriers affecting the drug absorption mechanisms should be carefully considered and the excipient related interactions of the efflux mechanisms could be utilized in modifying the drug absorption barriers and an improved oral bioavailability could be achieved. The prodrug approach for lipophilic drugs resulted in improved association with lipid digestion products and better absorption into the intestinal lymphatic system. The specialized structure and functions of the GALT allowed the delivery of several peptides and antigens by incorporation into particulate carriers. Though the particulate uptake is low, such low concentrations may be sufficient for stimulating the mucosal immune system. The intestinal tissue and the associated immunocompetent cells acts as a target for the potential antiviral agents like azidodeoxythymidine (AZT), as the HIV is considered to reside in the intestinal tissue in HIV infection.

A large number of animal models were utilized for estimating the intestinal lymphatic drug transport. Every model has its own advantages like ease of handling and relative simplicity of small animals such as rats, and more accurate reflectance of human physiology by large animals. Finally, the selection of animal models for the assessment of intestinal lymphatic drug transport is very critical and necessitates the consideration of a number of factors such as conscious status of the animal, site of cannulation and methodologies used for lymph collection, for better and effective comparison of data and reaching to definite conclusions.

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REDDY & MURTHY: LYMPHATIC TRANSPORT OF ORALLY ADMINISTERED DRUGS


