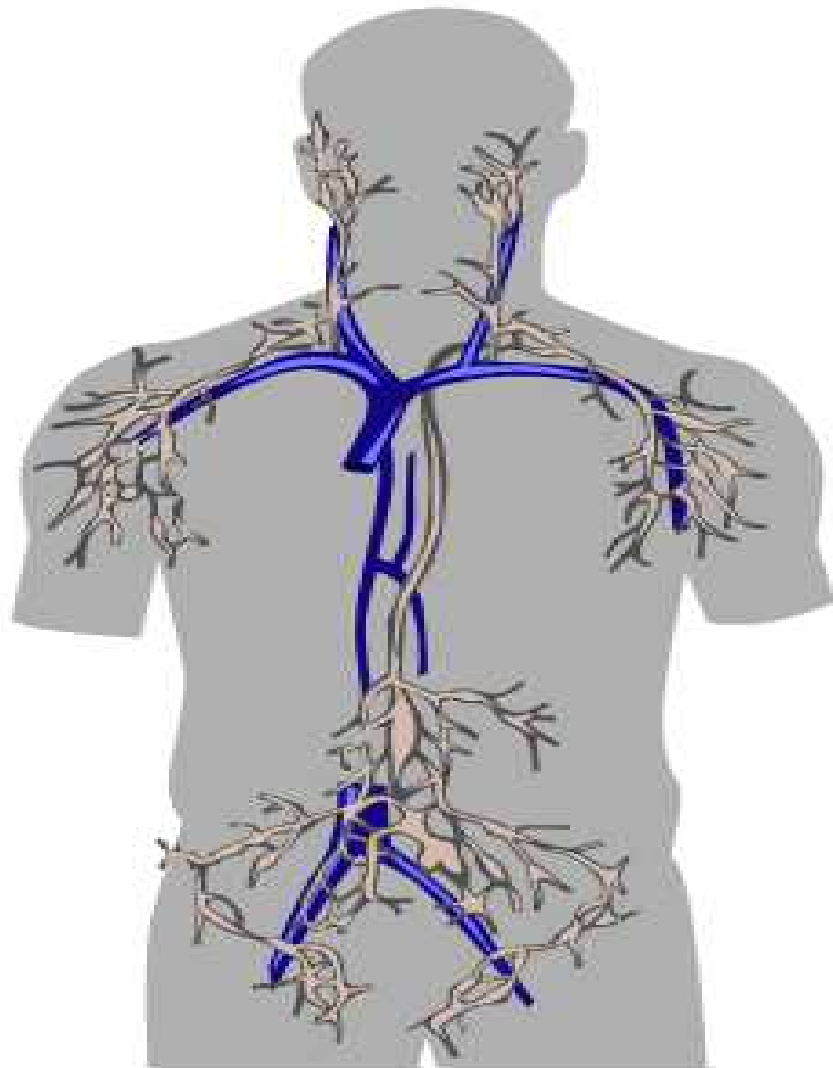


Lymphatic transport of drugs



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Lymphatic system

- Lymphatic system is closed system of lymph channels through which lymph flows.
- Lymphatic system is one way system and allows the lymph tissue spaces to the blood
- The lymphatic system can be broadly divided into the conducting system and the lymphoid tissue.
- The conducting system carries the lymph and consists of tubular vessels that include the lymph capillaries, the lymph vessels, and the right and thoracic ducts.

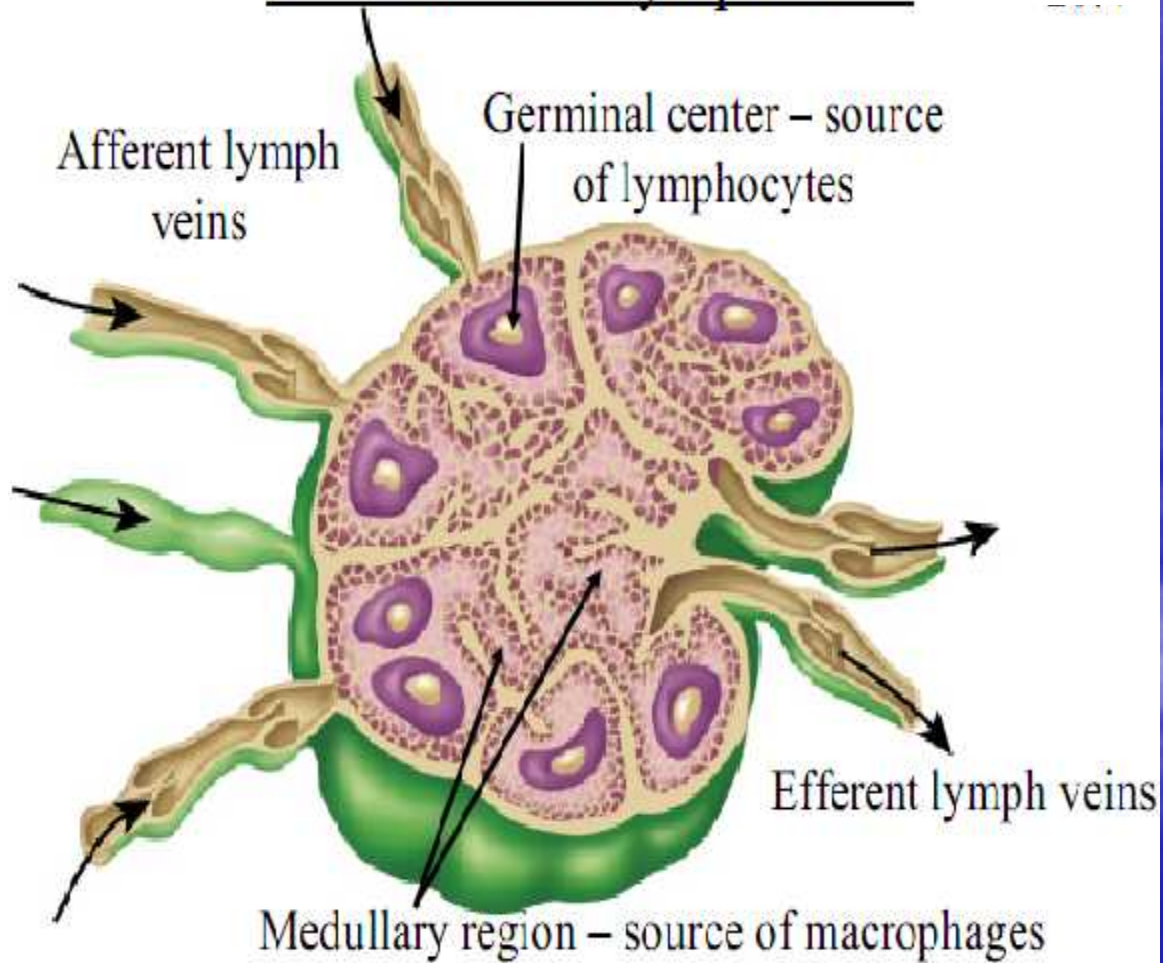
Lymphatic conducting system

- Tubular vessels transport back lymph to the blood ultimately replacing the volume lost from the blood during the formation of the interstitial fluid. These channels are the lymphatic channels or simply called *lymphatics*.
- lymphatic conducting system broadly consists of two types of channels—the *initial lymphatics* or *lymph capillaries* that specialize in collection of the lymph from the ISF, and the larger *lymph vessels* that propel the lymph forward

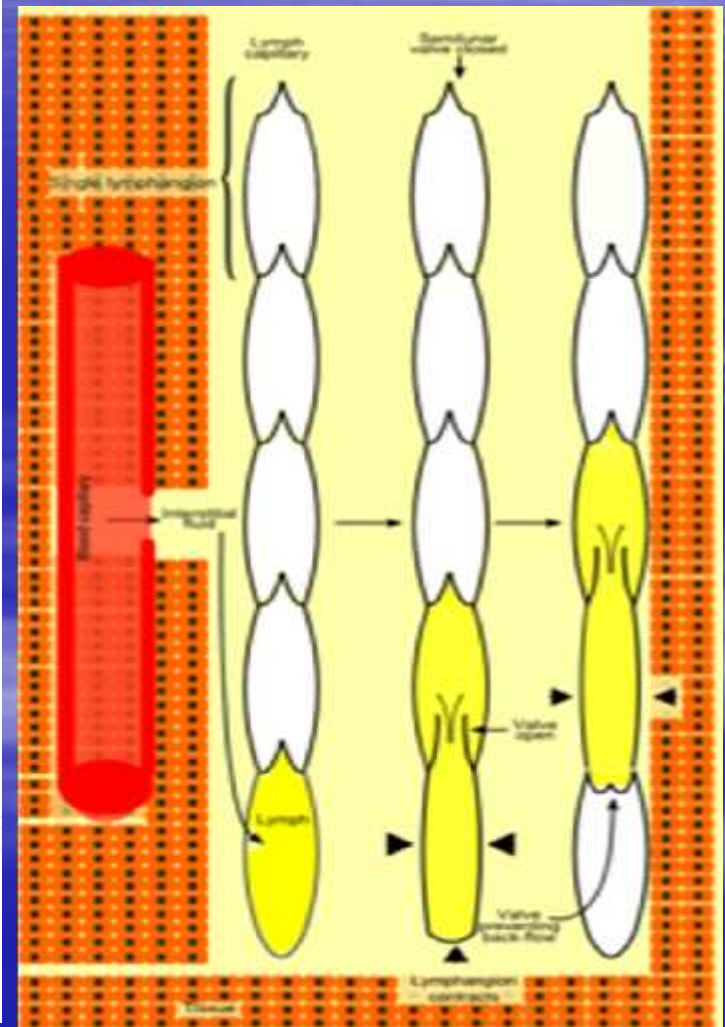
Lymphoid tissue

- Lymphoid tissue is concerned with immune functions in defending the body against the infections and spread of tumors. It consists of connective tissue with various types of white blood cells lymphocytes
- The lymphoid tissue may be primary, secondary, or tertiary depending upon the stage of lymphocyte development and maturation.

Structure of a Lymph Node



Lymph capillaries



Functions of the Lymph System

- 1) Maintains volume and pressure of extracellular fluid by returning excess water and dissolved substances from the interstitial fluid to the circulation.
- 2) Lymph nodes and other lymphoid tissues are the site of clonal production of immunocompetent lymphocytes and macrophages in the specific immune response.

Intestinal lymphatic drug transport

- Gastro intestinal tract is richly supplied with lymph and blood vessels, but majority of drugs are transported via portal blood than lymphatics.
- Highly lipophilic compounds, transport via intestinal lymphatics provides an additional route of access to the systemic circulation.
- **Examples:** cyclosporins, probucal, vitamin derivatives.

Advantages of intestinal lymphatic drug transport

1. Avoidance of hepatic first pass metabolism.
2. Selective treatment of diseases and infections of the mesenteric lymphatic.
3. Enhancement of absorption of large molecules such as peptides and particulates.
4. Inhibition of cancer cell metastasis.

Promotion of intestinal lymphatic drug transport

- Firstly ,the effect of changing the physico –chemical and biochemical properties of the drug via prodrug approach.
- Secondly ,the potential for enhanced lymphatic drug transport via formulation optimization is addressed.

Prodrug approaches for enhanced lymphatic delivery

- The design of lipophilic prodrugs is logical approach for enhancement of lymphatic transport.
- Prodrug approach is mainly used to increase the lipophilicity of the drug via the covalent coupling of drugs to lipid moieties including fatty acid, diglyceride or phosphoglyceride.
- Lipophilicity is most important physico chemical property necessary for lymphatic transport of drugs.
- The transport of lipophilic compound via intestinal lymphatic primarily occurs in association with chylomicron of intestinal lipoproteins.

- Ester or ether prodrugs are employed to enhance lymphatic transport and bioavailability.
- oral administration of lipophilic ester prodrug (testosterone undecanoate) resulted in increase in absolute bioavailability of testosterone.
- Aliphatic esters of fat soluble vitamins are synthesized to improve stability to enhance absorption via intestinal lymphatics.

Formulation approaches for enhanced intestinal lymphatic transport

- The requirement for drug association with intestinal lipoproteins as a prerequisite for drug transport via intestinal lymphatic has led to use of lipids and lipid based formulation to enhance lymphatic transport.
- Lipid based formulations may also enhance drug absorption via decreased gastric emptying rate, increased solubility of drug, formation of lipoproteins, increase in mucosal permeability.
- The efficiency of lipid digestion and solubilisation in the intestinal lumen and subsequent uptake and transport across intestinal absorptive cells is likely to significantly influence the access of lipophilic drugs to the lymph.

Choice of lipid / Formulation

- The choice of co-administered lipid is crucial determinant of extent of intestinal lymphatic drug.
- Lipids are characterized by
 - degree of lipid saturation,*
 - lipid chain length,*
 - lipid class.*
- Both the type and mass of co-administered lipid can alter the extent of lymphatic drug transport.

Fatty acid chain length of administered lipid

- fatty acids with chain lengths of 14 and above are absorbed directly into the thoracic lymph, whereas a larger proportions of the shorter chain lipids are absorbed directly into the blood.
- Lymphatic transport of exogenously administered increased in linear fashion after co-administration with triglycerides of increasing fatty acid chain length.
- DDT and probucol are highly lipophilic and lymphatically transported compounds.
 1. highest plasma concentrations were observed after administration in peanut oil.
 2. lowest plasma level were observed after administration in liquid paraffin.
 3. intermediate plasma concentrations were observed after administration in miglyol.
- Long-chain lipid vehicles proved to be more effective in promoting the lymphatic transport of retinoids than medium chain triglycerides.

Degree of unsaturation of administered lipid

- The degree of fatty acid unsaturation have large effect on the rate of absorption and partitioning of lipids between portal blood and intestinal lymph.
- lipids with increasing degrees of unsaturation appear to produce larger size lymph lipoproteins and preferentially promote lymphatic lipid transport.
- Improved absorption and intracellular transport of unsaturated lipids resulted from both improved digestion, and a more significant increase in lipid fluidity and corresponding decrease in lipid hydrophobic at body temperature,

Class of administered lipid (glyceride structure)

- Charman and Stella who examined the lymphatic transport of DDT in anaesthetized rats and reported a 2-fold increase in the cumulative extent of lymphatic transport of DDT after administration in a formulation comprising long-chain fatty acid C_{18} compared with the equivalent triglyceride-based lipid vehicle.
 - This is a result of the shorter time required for the synthesis of chylomicrons from the fatty acid vehicle when compared with the TG vehicle.

Lymphatic transport in the absence of co-administered lipid

- significant lymphatic transport may occur in the absence of co-administered lipid.
- Nishigaki et al. reported a 2-fold increase in lymphatic transport of retinyl palmitate after administration in an aqueous polysorbate 80 micellar solution compared with a lipid solution formulation.
- the lymphatic absorption of cyclosporin was found to be significantly greater (5–10-fold) after administration in a simple micellar solution formulation when compared with a lipid solution or mixed micellar formulations

The relatively high extent of lymphatic transport observed after oral administration in lipid-free formulations may be a function of

- (1) enhanced overall drug absorption occurring as a result of efficient solubilisation in the surfactant-rich formulations
- (2) enhanced drug absorption facilitated by the high surfactant concentration leading to a generalized increase in membrane permeability and
- (3) partitioning of drugs into lymph lipoproteins synthesized from endogenous lipids or the products of surfactant hydrolysis.

CONCLUSION

- Transport of orally administered drugs to the systemic circulation via the intestinal lymph may provide a number of delivery advantages including avoidance of first pass hepatic metabolism and site specific delivery to the lymphatics.
- Enhancement of lymphatic transport via formulation approaches may provide improvements in the relative bioavailability of compounds with very low absolute bioavailability.

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Thank you