IJPSR (2021), Volume 12, Issue 4 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 01 April 2020; received in revised form, 01 August 2020; accepted, 16 August 2020; published 01 April 2021

LYMPHATIC TARGETING SYSTEM USING NANO-FORMULATION: CHALLENGES AND APPROACHES

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Keywords:

Lymphatic Delivery, Lipid-based carriers, Nanocarriers

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ABSTRACT: The lymphatic system is the subpart of the systemic circulation for maintaining immune function; this system is mainly known as a drainage system to removes foreign bodies. This system consists of various lymphoid organs and tissues. The lymphatic system based on physiological function as absorption and micro-particulate uptake by these routes the bioavailability and efficacy were enhanced and undergone hepatic first-pass metabolism. The Lymphatic system is mainly used for the targeted delivery of chemotherapeutic agents; they also are modified for partial uptake into the lymphatic system to improve efficacy with the reduced systemic distribution. The anatomy and physiology of the lymphatic system, route of administration, physiochemical properties of drug carriers, and model for lymphatic uptake are also assessed; the novel system reviewed are SLN (solid lipid nanoparticle), liposomes, self-emulsifying system, polymeric micelles, dendrimers, carbon nanotube, hybrid nano-system, mesoporous silica nanoparticle. Lymphatic delivery employed various nanocarriers with the latest technology for various diseases to get a better therapeutic outcome.

INTRODUCTION: The lymphatic system was first accredited by Gasparo aselli in 1627, and the anatomy of the lymphatic system completely inscribe in the nineteenth century. The lymphatic word suggests itself as "lymph is a fluid that moves along with the circulatory system". The lymphatic system is a self-contained system within a large circulatory system also comprise of complex network channels that carry lymph to lymphoid tissues and organs; it is an irreversible one-way transit without application of driven force.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(4).2036-48

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(4).2036-48

The primary function of the lymphatic system is to regulate homeostasis and Immuno-functions and maintain the water balance by returning to systemic circulation to transport immune cells to lymph nodes [1, 2]. The lymphatic system plays a vital role in the absorption of long-chain fatty acid, triglyceride, and lipid-soluble vitamins. The delivery of drugs through the lymphatic way had an advantage to target drug to disease that spread through the lymphatic system also avoids the first-pass metabolism in the liver. The lymphatic system is a reservoir for the cancer cell to grow in lymph nodes, so various approaches are developed to overcome this situation.

Approaches of drug carriers investigated for lymphatic system include emulsion (penclomedine, darunavir) [3, 4], dendrimers (methotrexate) [5], micelles (Trp2 peptide, epirubicin) [6-8], liposomes (ritonavir, doxorubicin, asenapine maleate, OVA

antigen, paclitaxel) [9-13], solid dispersion (tacrolimus) [14], solid lipid nanoparticle (isradipine, doxycyline, ritonavir, efavirenz, curcumin, rifampicin, docetaxel) [15-21], Nano lipidic carrier (silymarin, tacrolimus, Orlistat, cabazitaxel) [22-25], SMEDDS (lurasidone hydrochloride, huperzine A, saquinavir, baicalein, silymarin, sirolimus) [26-31], SNEDDS (rosuvastatin, lopinavir, docetaxel) [32-34]. There are three ways for the delivery of drugs through the intestinal lymphatic vessel [35-36]. Firstly lymphatic capillary, which allows targeting of macromolecules for the lymphatic system, results in increases hydrophilic absorption with the help of an absorption enhancer [37]. Secondly, the peyer's patch, which provides the drug entry to the lymphatic system, and lastly third way was intestinal walls *via* transcellular absorption, which increased chylomicron production related to transport lipophilic compound into the lymphatic system. In this review, we are discussing the lymphatic system's various components, including anatomy also their physiological consideration for understanding their functions also the role of an intestinal lymphatic pathway for the oral digestion of lipid. Various physiochemical properties for the drug candidate which are targeted for lymphatic delivery are discussed in this review, including the size of particles, surface charge, lipid solubility, the concentration of surfactant. In these ways, the lymphatic system plays an essential role in immune activation or development of immune tolerance [38].

There was a wide diversity in the physiological function of a lymphatic system; they influence a wide range of diseases such as hypertension, atherosclerosis, liver disease, infection related to HIV; they have been failed for providing effective drug delivery through the conventional system.

Anatomy and Physiology of Lymphatic System: The lymphatic system is included as a part of the circulatory system and also plays a vital role in the immune system; it is made up of various individual parts in our body that work together to destroy phagocytes and to maintain our immunity strength. The lymphatic system is comprised of a network structure of the lymphatic vessel, and these vessels carried out fluid is known as˝lymph˝ . The other function of the lymphatic system as a drainage network that was spread throughout the whole body which is nearest to the circulatory system.

The lymphatic system handles 125 mL/h (2500-2800 mL of lymph/day) ~1/2 of this from the liver and small intestine alone. These systems consist of various organs and tissues such as lymphatic vessels, lymphatic nodes, spleen, thymus, peyer's patch, and tonsil. These organs and tissues are divided into sub-parts based on their function, such as primary lymphatic organs and secondary lymphatic organs; the primary lymphatic organs are those sites at which stem cells split-up and become immune proficient, it includes bone marrow, thymus. The secondary immune system is those where most of the immune response occurs, also consist of lymph capillaries, lymphatic vessels, lymphatic nodes, and spleen [39]. The lymphatic system is a one-way irreversible passage without driven force.

Primary Lymphatic Organs:

Bone Marrow: Bone marrow primarily consists of white blood cells, red blood cells and platelets. It is the main site for the production of immune system cells. Bone marrow is usually found inside the bone of the hip & thighs; bone marrow is also responsible for the designing of T cells and production and maturation of B cells; these T cells travel directly to the thymus for further development, and B cells travel to secondary lymphatic organs for the search of pathogens.

Thymus: The thymus is comprised of a typical type of white blood cell known as the T-cell. Found just below the chest bone, the thymus consists of lymphoid tissues and lymphocytes. Two distinct structures, the cortex, and the medulla work to push lymphoid cells from maturity into circulation within the body. The thymus is a primary lymphoid organ and the site of maturation for T cells, the lymphocytes of the adaptive immune system. T-cells that are critical to the adaptive immune system develop self-tolerance before being released into the body's system. The loss or lack of the thymus results in severe immunodeficiency and subsequent high susceptibility to infection [38].

Secondary Lymphatic Organs:

Lymphatic Capillaries: Lymphatic capillaries are called terminal lymphatic vessels, lymphatic capillaries in body tissues responsible for the reabsorption of excessive tissue fluid from where there was a diffusion of interstitial fluid and

through the lymphatic pathway it enters these capillary to be converted into lymph fluid. These lymphatic capillaries are interconnected with arterioles and veins of the systemic circulatory system. There are specialized lymphatic capillaries known as lacteals which are responsible for the absorption of short-chain fatty acid in the small intestine.

Lymphatic Vessels: Lymphatic vessel is similar to veins in terms of definition, but these lymphatic vessels slightly different structure to veins is that they have three tunic structure and presence of check valve the lymphatic vessel are of veins and also the presence of check valves. Check valves are present due to the function of lymphatic vessels to carry fluid under low pressure. The main function of these check valves is that they prevent the fluid backflow towards lymphatic capillaries. And at the interval of these vessels, lymph flows towards the lymph nodes.

Lymph Nodes: Lymph nodes are usually the cluster embedded in connective tissues these clusters occurs near the body surface in the axillary and cervical region these regions are the sites where lymphatic collecting vessel converge to form trunks lymph node and other lymphatic organs are tactics located sites where lymphocytes encounter antigens and are active to attack back against [1, 2].

Spleen: Spleen is an oversized lymph node located in the upper left abdominal part; it also works as a blood filter [8, 9]. The spleen structure is consists of red pulp and white pulp; in red pulp, there where filtration of red blood cells and remove the damaged cells from the body and white blood cells that fight against an antigen in the bloodstream because it includes T cells & B cells and responsible for immune response [39, 40].

Physiochemical Criteria for the Drug Candidate to Deliver Through Lymphatic System:

Particle Size of Drug and Carriers: The drug delivery through the lymphatic route mainly depends on the particle size, become the important factor in administering the drug through parenteral routes. If the particle is less than a few nanometers they get easily enter into the systemic circulation. If the fraction of nanoparticle is greater, they retained greater at the site and lesser enter into a lymphatic vessel also poorly transported to lymph; therefore, the size of nanoparticle ranging from 10-100nm for lymphatic delivery [38].

Surface Charge: Any drug which was delivered through the lymphatic system should have to pass through the interstitial fluid, so the study for a surface charge had been done on liposomes and proved that the negatively charged liposomes drained faster into lymph compared to positively charged liposomes after administered through intraperitoneal route [41]. Thus the order of liposome localization is in the order as negative > positive >neutral [42].

Molecular Weight: The compound which gets absorbed through the lymphatic system should have a molecular weight ranging from 1000-16,000Da. The higher molecular weight molecules are highly restricted for exchange across blood capillaries and also decrease the molecular uptake by the capillaries and increase the uptake in the lymphatic system at the site of injection. The molecular weight more than 16,000 which is to be absorbed by the lymphatic system rather than capillaries [2].

Lipophilicity: Lipophilic carrier molecules influence phagocytosis and its lymphatic uptake. Phagocytosis is more favored for lipophilic drugs. Lipid is considerable potential to transport through the intestinal lymphatic system; intestinal absorption is also affected by the types of lipids. It was proven that arachis oil increased the transport of drugs through the lymphatic route compare to another vehicle because arachis oil has long-chain unsaturated fatty acids, which increase the ability to stimulate chylomicron production[1].

Surface Modification: Surface modification provides scope for increasing the size of the drug molecule intended for lymphatic uptake. This approach holds great potential for targeting the lymphatic system. Surface modification can be achieved by using ligands like peptides, antigens or by using polyethylene glycol, biotin or surfactant [2].

Hydrophobicity: The hydrophobicity of the particle are directly related to surface properties which are responsible for lymphatic uptake [42]. Dahlback *et al*., had studied that the hydrophobicity of bacteria decrease phagocytes also increased in the opsonization process because the easily attracted towards hydrophobic surface rather than

hydrophilic surfaces increase lymphatic uptake [43, 44].

Types of Lipids: The nano-formulation is mostly lipid-based which is composed of triglycerides; these triglycerides are such that they arrange themselves that their polar heads are towards the aqueous phase; these types of arrangements are similar to chylomicron. The lipid based nano-scale formulation influences absorption in intestinal epithelial cells [45].

Lipid Solubility and Partition Coefficient: Lipid solubility and partition coefficient play an important role in transportation through the lymphatic system. Charman *et al.,* and Stella *et al.,* had demonstrated that triglyceride solubility and the log P value of drugs should be > 50mg/mL, respectively. They also compare the dichloro-diphenyltrichloroethane and hexachlorobenzene lymphatic transport having log P value 6.19 and 6.53 respectively, both the drug having different triglyceride solubility as a result Dichlorodiphenyl-trichloroethane has 13 fold higher solubility compare to hexachlorobenzene has been reported, so the conclusion was that the dichlorodiphenyl-trichloroethane had more lymphatic uptake than hexachlorobenzene the other authors Myers *et al.,* demonstrated that higher log P value increased the lipid solubility but not always result in increasing lymphatic uptake [46].

Routes for Lymphatic Delivery: The delivery through the lymphatic way is difficult due to poor absorption [47] in the lymphatic route, so to overcome these types of problems, various delivery systems are introduced, *i.e.,* colloidal systems like liposomes, polymeric Nanoparticle. These systems have the potential to deliver drug substances via lymphatic way through various routes; usually, there are four main ways to reach lymphatic vessels are intravascular, intra-lymphatic, intra-tissues, and intraluminal routes.

Oral Route: Gastrointestinal administration that corresponds to the intraluminal route [35]. This intestinal lymphatic system is especially for the absorption and transport of highly hydrophobic drugs and dietary fat. When the hydrophobic drug was taken orally, which result that the absorbed *via* the gastrointestinal route, and then the absorbed particle drained out in mesenteric lymph along through a thoracic duct and entered into the systemic circulation [38, 39]. As a result, to increase drug absorption into a body, hepatic first-pass metabolism should be avoided.

Mucosal Route: The target delivery to non-gastrointestinal mucosal lymphoid tissue, in that case, the delivery of vaccines via mucosal surface although these mucosal surface is varies from one site to another but have similar features related to lymphatic system M cells cover the MALT that transport antigen and particulate matter or macro-molecular drugs which are drained through mucosal lymph via lymphatic capillaries and vessels [38].

Parenteral Route: The interstitial administration (*via* subcutaneous, intramuscular, or intradermal route) the size of drug molecule usually be less than 10nm so that they enter into blood capillaries[38] rather than lymphatic capillary on another side of the particle size is more than 100nm resulted in reduced in diffusion and convection across interstitium, so they are not able to access through the lymphatic system. So that the drug molecule should be ranging from 10-100nm to enter the lymphatic system.

Hydrophilic molecules move effectively than hydrophobic molecules through interstitium so that the administration site also affect the extent of lymphatic transport the various studies had proved that the intradermal route has high uptake compared to intramuscular or subcutaneous [41].

Subcutaneous Route: For lymphatic delivery, the subcutaneous route has some advantages: the drug gets retained for longer at the administration site, increasing absorption and low clearance. If the nano-formulation was lipid-based and administered *via* these routes are not be directly reached to the systemic circulation because there was a restriction in the permeability of small molecules.

Also, the particle size of lipid based formulation affects the lymphatic transport via these route if the larger the particle, more the retention at the site and drug release slowly compare to small particle they easily access in the lymphatic system [48]. Wang *et al.,* studied that pegylated erythropoietin absorbed *via* these routes using the lymph duct cannulated

model result in 70-80% recoveries in excreta after the subcutaneous administration [49, 50].

Intradermal Route: Skin-related lymphoid have specialized cells that enhance the immune response. Sai *et al*., prepare the vaccine and conclude that the nanoparticle of 25nm easily accumulate in lymph node rather than the larger particle of a range 100nm after intradermal injection also revealed that these types of ultra-small nanoparticle result in complement activation formore immune response [51]. Also Puri *et al*., demonstrated microsphere had various varying factors like surface area if the larger the surface area low concentration of microsphere per injected site, which probably increases the interaction immune cells of the skin and produce an immune response. These results demonstrated that the immunization for the various micro-particulate delivery system had an effective means if they are administered *via* intradermal route [52].

Pulmonary Route: The pulmonary route has the potential for targeted delivery of SLN solid lipid Nanoparticle and also with certain types of cancer. Delivery targeted with SLN was mostly seen in the patient with lung cancer. The alveolar regions accept the particle of diameter 200nm for involvement in the lymphatic system [53, 55]. Videria *et al*., had prepared the SLN incorporated with paclitaxel and administered via an intravenous route; the formulation showed prolonged treatment without toxicity, so the SLN formulation was having high selectivity and low systemic circulation. The authors also demonstrated the uptake of SLN via a lymphatic system using radiolabeled SLNs, and the other researcher used these as a contrast agent in computed tomography.

Intestinal Route: Intestinal route was mostly preferred for the gastrointestinal tract because of its uniqueness in anatomy and physiology various factor related to anatomy and physiology included drug solubility, pH of the tract, and the retention time at the site affect its bioavailability to overcome these problems the SLN formulation incorporated with the drug to avoid first-pass metabolism [56]. Khan *et al*., demonstrated the incorporate idarubicin into SLN formulation in contrast with idarubicin solution *via* intraduodenal and intravenous route which result in enhancement of bioavailability *via* duodenal administration by 21 times compare to intravenous administration, which results in less distribution of a drug in kidney and heart so there were no chances of cardiotoxicity of idarubicin so that SLN was proved to be prolonged release system this SLN formulation also provide specific delivery increased in clinical efficacy and reduced toxicity of oral anticancer agents [57].

Novel Approaches in Lymphatic Delivery System: To deliver the drug via lymphatic system, this system mainly depended on the physiological process of lipid digestion also absorption of higher lipophilic drugs [35, 36] will move across the enterocyte to form chylomicron, these chylomicrons are drug-associated enter from a mesenteric duct to systemic circulation as a result hepatic first-pass metabolism was avoided by the high lipophilic drug **Fig. 1**. If the drug has first-pass metabolism, the bioavailability of that drug improved by absorbing in the intestine by using the lymphatic system so various types of a lipid-based nanoparticle can be done to mimic the physiological condition favorable for lymphatic drug delivery [41].

SLNs (Solid Lipid Nano-particles): Solid lipid nanoparticles (SLNs) are lipid-based drug carriers that remain solid at room and body temperatures. Lipids utilized for SLNs are typically physiological lipids, including fatty acids, steroids, waxes, and mono-, di-, or triglyceride mixtures. SLNs are composed of a lipid core that stimulates the formation of chylomicrons, which transport the carrier and associated drug *via* the classical trans-cellular mechanism of lipid absorption[42]. This process increases the absorption of drugs into the lymphatic system. SLNs also have the potential to allow controlled drug release and drug targeting, increased drug stability, and high drug payload. Additionally, SLNs are being used increasingly for the protection of labile drugs from degradation in the body and sustained release [3, 4]. Truzzi *et al*., focused on the antitumor effects through lymphatic circulation, using solid lipid nanoparticles (SLNs) to encapsulate iron oxide nanoparticles and heparin to simulate the intestinal lymphatic absorption of oral administration in CaCo-2 cells [58]. This approach demonstrates that SLNs can be used as an important route of delivery for oral administration.

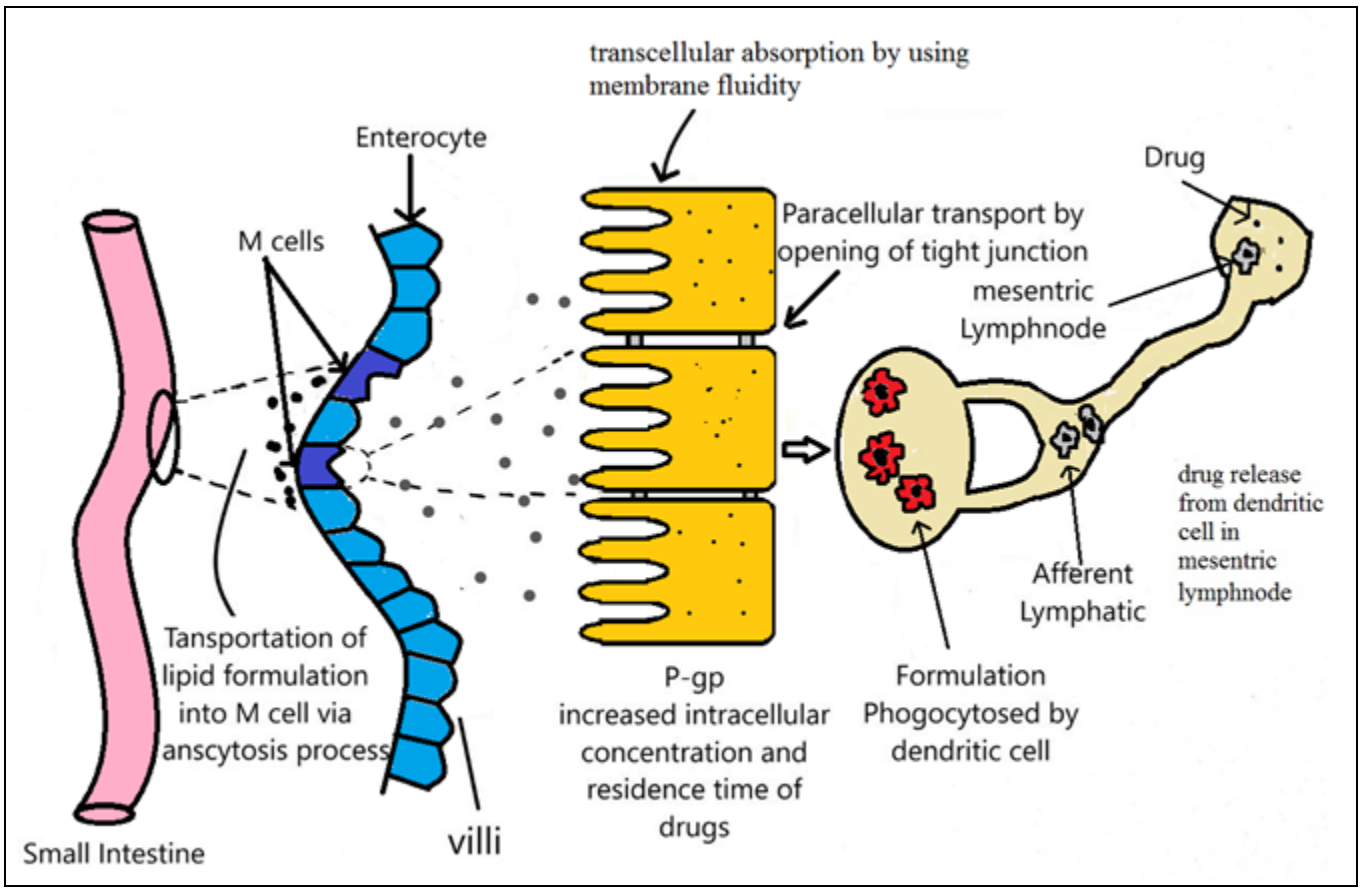

FIG. 1: SCHEMATIC REPRESENTATION OF INTESTINAL TRANSPORT OF LIPID-BASED FORMULATION MECHANISM *VIA* A PORTAL AND MESENTERIC LYMPHATIC ROUTES

Liposomes: Liposomes are the lipid bilayer structured potentially useful for efficacy lymphatic drug delivery because of its ability to enhance permeability across the enterocyte to stabilize drugs and provide the controlled release pattern [1]. Also besides, liposomes as nanocarriers of chemotherapy drugs have also been used in breast cancer, ovarian cancer, and Kaposi's sarcoma treatment and achieved good results [53, 59]. Recently, the liposomes have been used to target CD45 and/or CD90 of T-cells *in-vitro* and *in-vivo* to realize adoptive immunotherapy [56]. Liposomes have recently been used to deliver the drug into the inner ear to overcome the blood-cochlear obstacle and round window membrane and provide a promising efficacy for inner ear disease [60]. Wang *et al*., modified doxorubicin-liposome (DOX-liposome) with polymethacrylate derivatives (DOX-ERLP). The *in-vitro* study on MCF7/ADR cells and liver cancer H22 cells showed DOX-ERLP can cause cancer cell death efficiently, and the *in-vivo* study on H22-bearing mice presented an obvious cancer cell apoptosis and necrosis compared with control groups [61].

Polymeric Micelles: Polymeric carriers are used to achieve the lymph targeted drug delivery; they are generally of two categories natural polymers and synthetic polymers [2]. The polymeric nanoparticle size depends on the method of synthesis [62] in these methods, either the drug gets entrapped, or conjugate with polymer, the approaches of biodegradable polymer is increasing, and toxicity are minimized, so they are extensively used for lymphatic targeting [48]. Liu *et al*., designed poly-(lactic-co-glycolic acid) nanoparticles modified with transferrin to use it as a carrier for DOX and then targeted the nano-medicine to leukemia K562 cells showing high expression of transferrin receptor; the result showed that the effect of DOX on killing tumor cells was significantly increased. Li *et al*., had demonstrated good stability, efficient cellular uptake, and cytotoxicity of DOX-loaded copolymers on Hela cells and COS7 cells by *in-vitro* tests [63]. Nam *et al*., constructed a novel nanocarrier based on the mussel-inspired mineralization using calcium phosphate-assembled polymer nanocarrier to load DOX.

A series of analyses and *in-vitro* tests in SCC7 cells proved that the nanocarrier has good stability, high cellular uptake, and low toxicity and may be used in the delivery of many hydrophobic antineoplastic drugs in the future [64].

Dendrimers: These formulation having versatile properties, homogenous size; the feature of the dendrimer is usually globular with changeable functional groups that are responsible for interaction with the environment also attach to the surface and modulate the solubility and toxicity. Dendrimers have significant potential as chemotherapeutic delivery vectors for passive and targeted delivery to tumors. Nguyen *et al*., studied letrozole-loaded poly(amido-amine) (PAMAM) dendrimer G3.5 coated Hep by an *in-vitro* release test, which showed a potential drug release ability of pH- and redox-responsive PAMAM dendrimers [65]. This study indicated that dendrimers could be used as effective Nanocarriers. Zarebkohan *et al*., developed a PAMAM-PEG-serine-arginine-leucine (SRL) nanocarrier to target C6 glioma. In *in-vitro* tests, GFP, green fluorescence protein (GFP)-loaded dendrimer showed specific target ability, which indicated PAMAM-PEG-SRL nanocarrier had the potential to be used for gene delivery to overcome BBB barrier and brain diseases [66]. Also, it is reported that dendrimers have been applied for psoriasis skin treatment in an *in-vitro* study [67]. Soibermon *et al*., used G4-PAMAM dendrimer to deliver dexamethasone for corneal inflammation. An *in-vivo* study in a rat mild alkali burn model showed dendrimer to be a potential drug delivery platform for corticosteroids to address sustained delivery and enhanced bioavailability for eye diseases [68].

Carbon Nanotubes: These are cylindrical nanostructured with coaxial graphite layers [69]. They possess various properties like high surface area, mechanical strength, thermal and chemical stability which make them versatile carriers for drugs, proteins, and peptides, radiological. For effective lymphatic delivery, hydrophilic multi-walled carbon nano-tubes MWNT and coated with magnetic nanoparticle (MN-MWNT) had emerged when Yang *et al*., administered these (MN-MWNT) drug loaded in rats, they found the maximum concentration of drug in lymph nodes [70]. Dong *et al*., explored the potential of MWCNTs-transactivator of transcription-chitosan (TC) as carriers of DOX against BEL-7402 cells in vitro, which demonstrated that this drug delivery system had good treatment efficacy on cancer and revealed its application potential for cancer therapy. It is well known that CNTs play an important role in gene therapy [71]. Huzil *et al*., compared metallic SWCNTs single-walled CNTs with semiconducting CNTs on SiRNA delivery; the results in murine PAM212 keratinocytes showed that metallic SWCNTs can be transferred into the nucleus, while the transport of semiconducting CNTs was limited since they could only enter the cytoplasm [72]. This result suggests that metallic SWCNTs single-walled CNTs can provide a specific target to the nucleus and has a potential to apply in gene delivery Iannazzo *et al*., reported that MWCNTs multiwalled CNTs modified by hydrophilic moieties at free carboxylic groups induce a better water dispersibility, which is relevant for the interaction between biological tissue and Nano-materials [73]. Both Bianco *et al*., and Pistone *et al*., highlighted that the biocompatibility, biodegradability, and release ability of CNTs can be modified by the surface functionalization (*e.g.*, hydrophilic PEG chain) and the introduction of structural defects) [74, 75].

Nano-capsules: These are colloidal drug carrier systems composed either of oily or aqueous phases surrounded by a polymer membrane. These carriers have some advantage as they protect the exposure of the drug to the external environment due to encapsulation of the drug; these capsules are coated with hydrophobic polymer so it can easily be taken up by lymphatic cells Nano-capsules are retained more in the right iliac regional lymph nodes as compared to the conventional dosage form. Abellan *et al*., observed that reducing the size of Nano-capsule encapsulating docetaxel from 200 nm to 100 nm further increased the lymphatic drainage [76]. Singh *et al*., demonstrated Nano-capsules coated with hydrophobic polymers could be easily captured by lymphatic cells in the body when administered because the hydrophobic particle is generally recognized as a foreign substance. The lymphatic targeting ability of poly isobutyl-cyanoacrylate Nano-capsules encapsulating 12-(9-anthroxy) stearic acid upon I.M. administration was evaluated and compared with three conventional colloidal formulations[77].

An *in-vivo* study in rats proved that poly isobutylcyanoacrylate that are retained more in the iliac regional lymph nodes as compared to other colloidal carriers.

Mesoporous Silica Nanoparticles: According to the different preparation processes, mesoporous silica nanoparticles (MSNs) can have a variety of shapes and sizes [78]. Gao *et al*., used different sizes of MSNs to carry DOX, and then used them against drug-resistant breast cancer cells (MCF-7/ADR); the results suggested that the antitumor activity of MSNs showed a dependence on the pore size [79]. The larger pore size of MSNs can make the cancer cells absorb DOX faster so that the rapid accumulation of intracellular drugs plays a strong role in the reversal of MDR. MSNs as a carrier for targeted therapy had great potential for overcoming MDR. Su *et al*., reported that red blood cell membrane-coated MSNs loaded with DOX and chlorine, which form a new type of nanoparticle, can produce a longer cycle time, good imaging effect, sustained drug release, as well as an obvious anticancer effect in 4T1 breast cancer mouse model [80]. In most cases, MSNs are used to encapsulate small hydrophobic drugs, but the recent use of transport gene sequences has become a new research focus [81]. Biswas designed an MSN carrier to deliver valsartan (VAL). The MSNs were modified by aminopropyl groups and pH-sensitive polymer Eudragit L 100-55. The *in-vitro* tests showed that this combination of nanoparticles and VAL has good solubility and higher bioavailability compared to the individual drugs, and the *in-vivo* tests on rats showed this Nano-drug can lead to more sustained antihypertensive effects [82].

Hybrid Nano-System: Hybrid systems a combination of two or more delivery forms for effective targeting. Feng *et al*., developed liposomes containing diethylaminoethyl-dextran, which substantially reduced the undesired local retention and promoted the draining of liposome into rat lymphatics after S.C. injection. Van der Lubben *et al*., prepared and investigated the in vivo efficacy of plasmid DNA loaded chitosan NPs for nasal mucosal immunization against hepatitis B. Chitosan DNA NPs were prepared by the coacervation process [71], in which chitosan-DNA might be taken in by M cell, and transported across the mucosal boundary, thereby transfecting immune cells within nasal associated lymphoid tissue (NALT) or gut-associated lymphoid tissue (GALT) both as immunoglobulin A (IgA) inductive sites [72].

Models for Lymphatic Delivery:

***In-vivo* Models:**

Animal models: For the *in-vivo* lymph duct, various cannulated animal models are used including rats, dog, mouse for lymphatic delivery. Porter *et al.,* had taken advantage of for conscious rat model and allows the oral and intraduodenal administration and these experiment conduct in the absence of anesthesia which proved that the reduced lymph flow was avoided. Khoo *et al.*, demonstrated the contrast dog model versus rat model and administered the dosage form size similar to human, as a result, it was not possible in rats due to continuous bile flow and also pulsatile response due to the presence of food in dog, and these were absent in human.

***In-vitro* Models:**

Intestinal Permeability Model:

Caco-2 Cell Line Study: The *in-vitro* models for permeability studies mainly suggested as a screening tool for accessing properties of new chemical entities. Stephen *et al.,* had reviewed the perspective that had encountered during the assaying the permeability of poorly soluble drugs and suggested cellular and Non-cellular models [83]. The $CaCo_2$ model was treated with alcohol to observe that alcohol induces intestinal barrier dysfunction and decreased the expression of Zonula Occludens Zo-1 also claudin-1. The result was alcohol decrease the expression depends on the changes in dose or behavior, thus increase the intestinal epithelial barrier permeability [84]. Sahu *et al*., suggested that there was a cytotoxicity effect of silver Nanoparticle in cultured $HepG_2$ and $CaCo_2$ cells, which provide the mechanistic information of that it was safety assessment of food and cosmetic related silver Nanoparticle the result showed that $HepG_2$ cells are highly responsive compare to $CaCo_2$ cells for silver Nanoparticle [85] .

Lipolysis Model: Dahan *et al.,* had demonstrated this model is used to evaluate IVIVC (*in-vitro in-vivo* correlation); it was also used as a predictive tool to evaluate the influence of various vehicle on oral absorption of lipophilic drug; they also studied

that *in-vitro* lipolysis and *ex-vivo* permeability data were used to predict the *in-vivo* bioavailability by incorporating different lipid-based formulation in rats also utilized the dissolution studies of dexa-methasone and griseofulvin in various triglyceride formulation in dynamic *in-vitro* lipolysis model. The result showed that various formulations of dexamethasone and MCT4LCT4SCT4H_2O for grivesofluvin have equivalent performance in the *in-vitro* lipolysis model. On the other hand, *in-vivo* data are compared with *in-vitro* data for both the drugs are equal. And finally, it was revealed that the lipolysis model is used to enhance intestinal permeability by formulation [66].

Application of Lymphatic Delivery:

Cancer: The lymphatic plays a vital role in cancer metastasis; the major cause for the spreading of the tumor was a wide distribution of lymph nodes. The lymph nodes are the major sign of the development of many cancer. The lymph node metastasis was usually observed in the patient with lung cancer, esophageal cancer, and other thoracic tumors they are facing problem to eliminate tumor cells from lymphatic regional hence there was the development of drug delivery system that would efficiently distribute anticancer agents and proved as an attractive therapeutic approach. Liu *et al.,* point out the role of the lymphatic system to drain out particulates from the intestinal tissue and demonstrated that the use of the colloidal system as targeting agent to regional lymph nodes after the administration they observed that particle does not enter the systemic circulation but the pass-through lymphatic vessel due to difference in permeability. Drug Delivery *via* the lymphatic system possesses enormous potential for the control and avoidance of early state cancers [35]. Fan *et al.,* studied a conjugated nanoparticle of follicle-stimulating hormone polypeptide nanoparticle loaded with paclitaxel (FSHP-NP-PTX) to target ovarian cancer; they observed that (FSHP-NP-PTX) provide the strong, stronger anti-proliferative action and *in-vivo* examination showed that reduce in size and weight of lymph nodes were reduce by (FSHP-NP-PTX) [6].

HIV: HIV is found in blood with more amount of mononuclear cells located in the lymph node. In the case of lymphedema, there will be an obstruction in normal lymphatic channels which interferes with the lymphatic flow, which resulted in the removal of antigen and weakened immune response. Horiike *et al.,* suggested that for the highly active antiretroviral therapy that lymphatic tissue, including mesenteric lymph nodes, plays a major role in the cellular reservoir [86]. Fletcher *et al.,* observed that the concentration of antiretroviral drugs in the patient is directly correlated with the effectiveness of antiretroviral suppression in lymphoid tissue [87]. Thus delivery through lymphatic route will enhance the therapy against viruses that reside and distribute *via* lymphatics; therefore, lymphatic targeted delivery now being increasingly focused on enhancing antiretroviral activity, so the range of nano-medicine platforms are used to facilitates the delivery of antiretroviral to HIV reservoirs in lymphoid tissue [88].

Filariasis: In the life cycle of parasite organisms, the key elements are lymph nodes. In a chronic infective state, the immunological mediated inflammation results in severe lymphatic destruction, and the adult worms carry by lymph nodes that block the lymphatic drainage result in severe swelling in limbs were observed. The current treatments for filariasis are not that effective because they reside deep in the human lymphatic system. Ali *et al.,* reported the improvement of anti filariasis activity by using chitosan-alginate nanoparticles loaded with ivermectin; by providing treatment with these nanoparticles, the microfilaria is disappeared in 60 days. Hence, the conclusion was to enhance the localization of anti-filarial by surface modification of polymeric nanoparticles to improve lymphatic targeting [89.]

Immunomodulation: The lymphatic system delivers the immune cells such as T cell and B cell according to the studies, the concentration of both types of immune cells are high in lymph than that in blood [90]. Hence, for the immune-modulatory drug, the lymphatic delivery is an attractive route; therefore the oral route for lymphatic delivery becomes more accurate, which induces higher efficacy and lower side effects.

Tuberculosis: Tuberculosis is caused due to special species of mycobacterium tuberculosis there was also different type of tuberculosis in which the lymph node TB is a most common form

of extrapulmonary which spread from lungs to lymph nodes also spread to other parts, therefore, the researcher suggests that using liposomes target the anti-tuberculosis drug which will directly reach to lymph node and help to manage disease [91].

Anthrax: Anthrax infection is caused by bacillus anthracis species; these are the bacteria present in the body are engulfed by macrophages they are transported to lymph node and transform into vegetative bacteria [70]. The treatment of these diseases is difficult due to the location of mediastinal nodes due to which external beam radiation is difficult to target; also other reasons that there was limited access of drugs to mediastinal nodes.

Leishmaniasis: Leishmaniasis is the protozoan parasites that reside in macrophages, and after getting a release in blood, they become motile. To stop the progression of disease maturation site of macrophages is targeted, because of the higher concentration of macrophages in lymphatics, so the lymphatic targeting is proved as a fruitful delivery system.

The novel treatment for anti-leishmaniasis is ambisome is only the drug available in the market which is of too high cost also having stability problem, so various colloidal system are exploited like micro and nanoparticle for actively and passively delivery using a range of anti-leishmaniasis drugs and polymers [92- 94].

CONCLUSION: Lymphatic transport is complex process these systems offer potential targeted drug delivery, particularly the lymphatic system plays an important role in cancer progression also provides novel targets for anticancer treatment. Various nanoparticle for lymphatic delivery is exploited discussed in this review. The uptake and distribution of carriers in the lymphatic system are demonstrated, which are directly dependent on the physicochemical properties of drug candidates to move across the lymphatic system and administration routes. By understanding lymphatic transport and its uptake, one can design new treatment for effective disease control.

ACKNOWLEDGEMENT: The authors are thankful to Ramanbhai Patel College of Pharmacy for providing the infrastructural facilities.

CONFLICTS OF INTEREST: The authors declare no conflict of interest.

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How to cite this article:
Desai J and Patel T: Lymphatic targeting system using nano-formulation: challenges and approaches. Int J Pharm Sci & Res 2021; 12(4): 2036-48. doi: 10.13040/IJPSR.0975-8232.12(4).2036-48.

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