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Novel Modified Nanosystem Based Lymphatic Targeting

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ABSTRACT

Targeting of drugs and bioactives to lymphatic system is very challenging and it depends upon the complex physiology of the lymphatic system. Targeting helps in achieving the aim of direct contact of drug with the specific site, decreasing the dose of the drugs and minimising the adverse effects caused by them. Use of nanosystem has promoted the lymphatic targeting; but still there are challenges of detecting specific sites, maintaining desired action, crossing all the physiological barriers. These hurdles could be overcome by the use of modified nanosystems achieved by the surface engineering. This review provides a summation of physiology of lymphatic system, different physicochemical parameter and their effect on lymphatic system, solute uptake by lymphatic system, different lymphatic targeting areas, strategies for surface engineering, different techniques of surface modification, detail of work done related to the drug delivery systems for lymph targeting like liposomes, nanoparticles, nanocapsules etc. This review will provide a platform for researchers working in this area of treating abnormalities related to lymphatic system with new approach of surface modification of various novel nanosystems.

Key words: Modified nanosystems, surface engineered, lymphatic drug delivery, ligands, lymphatic physicochemical parameters

INTRODUCTION

In the past few decades, rapid advances in cell and molecular biology have allowed us to develop a better understanding of the pathophysiology of various diseases. This has cast a floodlight on the possible cellular and molecular targets which can be exploited not only for drug discovery but also for imaging and therapy (Vasir *et al.*, 2005). One of the challenges to application in various areas, for example, in biomedical systems as well as medical therapy and diagnosis, lies in the engineering of a robust, tailored surface functionality ensuring biocompatibility and allowing specific site targeting. Several methods have been developed to modify the surface properties of the microparticulate system (Bumgarner *et al.*, 2009) microspheres (Robinson and Lee, 1987), nanospheres (Moghimi, 2003), nanoworms (Park *et al.*, 2009), nanoparticles (Behrens *et al.*, 2006), liposomes (Rawat *et al.*, 2008), cells (Mitsuyoshi, 2004), lipospheres (Rawat and Swarnlata, 2008) synthetic gene delivery vectors (Lee and Schaffe, 2002), suitable for attachment of functional, bioactive groups. Broadly Surface engineering is the sub-discipline of materials science which deals with the surface of solid matter. It has applications to chemistry, mechanical engineering and electrical engineering (Kovalenko and Kovalenko, 2000; Chattopadhyay, 2001). Interest in this concept has increased significantly in recent years with the advent of new technology and better understanding of the processes involved in drug delivery both at cellular and sub-cellular levels. Drug delivery systems may function through their ability to recognize certain types of target cells. However, the challenge with these drug delivery systems is that they are treated as foreign by the host when injected and end up mainly in the cells of the RES, namely macrophages of the liver, spleen, lungs, bone marrow and lymph nodes. Surface engineering of colloidal carrier systems allows them to selectively extravasate in pathological sites, such as tumors or inflamed regions with a leaky vasculature (Sahoo and Labhasetwar, 2003). An ideal targeted drug delivery approach would not only increase therapeutic efficacy of drugs but also decrease the toxicity associated with drug to allow lower doses of the drug to be used in therapy. The design of suitable carrier system and their surface modification that could be able to deliver the drug to its target site (Vasir *et al.*, 2005). In the case of drug delivery particles, these actions result in the foreign device being quickly and efficiently removed from the body. Many drug-delivery systems implement selective interactions; poor biocompatibility remains a major problem for other drug-delivery techniques. An appropriately designed controlled release drug delivery system can be a major advance towards solving problems concerning the targeting of a drug to a specific organ or tissue and controlling the rate of drug delivery to the target sites (Khan, 2001). In recent years surface biomedical engineering has taken two approaches: Increasing the biocompatibility of such engineered surfaces and promoting selective interactions for the use in immuno sensors and drug targeting systems (McGurk *et al.*, 1999). Main hurdles to drug targeting include physiological barriers, biochemical challenges to identify and validate the molecular targets and the pharmaceutical challenges to devise appropriate techniques of conjugating targeting ligands to the nanosystems. The challenge in drug targeting is not only the targeting of drug to a specific site but also retaining it for the desired duration to elicit pharmacological action. The *in vivo* bio distribution and opsonisation of nanosystems in blood circulation is governed by their size and surface characteristics. The passage of drug molecules and drug delivery systems across the endothelium is sensitive to the molecular weight and size of the system, respectively (Vyas and Khar, 2006).

THE PHYSIOLOGY OF LYMPHATIC SYSTEM

The lymphatic system was first recognized by Gasparo Aselli (Chikly, 1997). The lymphatic system is a drainage system, collecting and returning intestinal fluids. As with the blood network the lymph vessels form a network throughout the body, unlike the blood the lymph system is a one-way street draining lymph from the tissue and returning it to the blood. This system is a network of capillaries and tubes called lympahtics. The main components of the lymphatic system are bone marrow, lymph nodes, spleen and the thymus gland. There are five main categories of conduits in the lymphatic system: the capillaries, collecting vessels, lymph nodes, trunks and ducts. Their sizes range from 10 to 2 mm in diameter. Lymphatic capillaries are 10-60 mm in diameter and are comprised of one endothelial cell layer, typically made up of one or two nonfenestrated, highly attenuated cells in cross section. They have a discontinuous or absent basement membrane and with the exception of the initial lymphatics in the bat's wing, are non-contractile. All collecting vessels pass through lymph nodes which are capsular and organized in clusters through-out the lymphatic system. There is hundreds of lymph nodes in the adult human body and vary in size from 1 to 10 mm in diameter. Lymphocytes develop in the thymus gland or in the bone marrow. Lymphocytes in the lymph nodes aid the body in fighting infection by producing antibodies that destroy bacteria and viruses. The main functions of the lymphatic system are fluid and protein balance, immunity and spread of infection, digestion and solute uptake (Swartz, 2001).

Figure 1 shows that particles up to 100 nm in diameter are preferentially transported into the lymph capillaries and phagocytised in the lymph nodes.

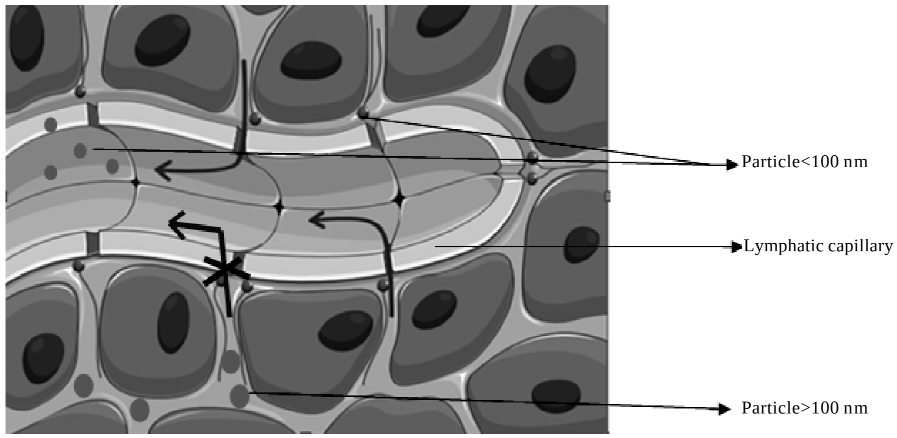

Fig. 1: Effect of particle size on lymphatic transport

SOLUTE UPTAKE BY LYMPHATIC SYSTEM

The uptake of inert particulate matter (as opposed to viral/bacterial uptake) by the gastrointestinal epithelium and peripheral lymphatic duct are now a widely accepted phenomenon and has prompted a number of biotechnology companies and researchers to focus on this route for the delivery of gastrointestinal (GIT) labile molecules, anti-HIV, anti-cancer and immunosuppressant drug using micro particulate carriers (Hussain *et al.*, 2001). The endothelial cell junctions of the initial lymphatics are not tight and considered freely permeable to most proteins, the physicochemical properties of the extracellular membrane can affect interstitial solute transport. Since, the solute must travel at least some distance through the interstitium before entering the lymphatics, the interstitial resistance to molecular transport greatly affects the apparent lymphatic uptake rate. Furthermore, significant changes in lymph concentration occur as the fluid passes through various components of the lymphatic system. It becomes concentrated along the contracting lymphangion segments, possibly due to water filtration across the vessel wall. Then, protein concentration decreases during its residence in the lymph nodes from osmotically driven fluid exchange with nodal blood vessels and phagocytosis by white cells. The issue of protein sieving during lymphatic uptake is somewhat controversial. The endothelium of the initial lymphatic poses very little hindrance to solute uptake and when fluid colloid osmotic pressure is directly compared locally between the interstitium and the initial lymphatic vessels, little to no differences are seen. Interstitial protein concentration is inversely related to trans vascular fluid flux and/or blood pressure and lymph protein concentration reflects interstitial protein concentration. The size, shape, charge and lipophilicity of a molecule affect its uptake rate into the lymphatics may actually reflect its interstitial hindrance prior to lymphatic uptake (Porter and Charman, 2001b; Hawley *et al.*, 1995; Liu *et al.*, 2006). Indeed, interstitial transport cannot be easily decoupled from lymphatic uptake and the path through the extracellular matrix to the lymphatics should be considered when interpreting uptake data for proteins, colloids, drugs, or drug carriers. For the remainder of this discussion, the term lymphatic uptake will refer to the coupled process of interstitial and translymphatic transport, recognizing the importance of the interstitium and its physicochemical properties and architecture in controlling molecular transport. Size is one of the most important determinants of lymphatic uptake and lymph node retention. Molecules that are smaller than 10 nm are preferentially reabsorbed into the blood capillaries while the optimal size for lymphatic uptake is between 10 and 100 nm. The larger the particle or molecule, the more is the selectivity for uptake into the lymphatic system but the slower the uptake. For example, liposomes of 30-60 nm were found to have faster uptake rates than those of 400 nm but the smaller ones also showed higher level in the blood circulation. The upper size limit for lymphatic uptake has not been strictly defined. Particles up to 1 mm have been taken up by the lymphatics following interstitial injection; but above 100 nm, a percentage of injected solute will remain trapped in the interstitial spaces for longer periods of time and thus have lower uptake efficiencies. The composition of the molecule or particle is also important in determining uptake and lymph node retention. Colloids and lipids seem to have high uptake efficiencies. Depending on the size, charge, method of preparation and composition, various molecules such as monoclonal antibodies, peptide drugs and anticancer agents may be encapsulated into liposomes, nanoparticles, dendrimers etc and optimally targeted to lymph nodes (Gref *et al*., 2000; Semwal *et al*., 2010; Luo *et al*., 2010). Furthermore, the microparticulate systems can be coated (e.g., with polyethylene glycol) or surface engineered with specific Ligands/chemicals (e.g., Folic acid, Lectin, L-selectin etc.) to improve lymph node retention by avoiding white blood cell phagocytosis; such stealth liposomes are well-characterized and can be designed for a number of specific purposes. Other than intercellular pathways, there is ample evidence for transendothelial pathways for solute and lipid transport in the initial lymphatics. After food uptake, lymphatic endothelial cells may be able to phagocytose particular matter and 7-8 mm trans endothelial channels were seen following milk lipid adsorption. Furthermore, these trans endothelial channels seem to be permanent structures since they are found even after periods of fasting (Ohhashi *et al*., 2005).

LYMPHATIC TARGETING AREAS

The lymph as a therapeutic target, number of specific investigations of drug delivery or drug targeting to the lymphatics is much more modest. This may reflect the historical belief that the lymphatics play a minor role in drug absorption (which indeed is the case for the majority of hydrophilic or moderately lipophilic small molecules), however recent results from this and other laboratories suggest that under certain circumstances, the lymphatics may provide the primary route of drug absorption and lead to drug concentrations in the lymph some 5-10,000 times higher than in systemic plasma. Recent advances in drug design and delivery, have also led to the development of an increasing number of (1) highly lipophilic drug molecules which may be substrates for intestinal lymphatic transport, (2) macromolecular biotechnology products which appear to be absorbed into the peripheral lymphatics after SC injection and (3) a range of particulate colloidal systems (micro particles, lipid carriers etc.) (Saraf *et al*., 2011) which may facilitate the lymphatic transfer of drug molecules with little intrinsic lymph-directing capacity. Recent data that suggests that for some compounds intestinal lymphatic transport may be both the primary route of absorption and responsible for the transport of the majority of the drug dose to the systemic circulation (Porter and Charman, 2001a). The lymphatics are the primary conduit for the dissemination of metastases from many solid tumors, play a pivotal role in the generation of immune responses and have been implicated in the pathogenesis of diseases including HIV and metastitial tuberculosis. For lymph resident diseases, lymphatic targeting of therapeutic drugs (e.g., antivirals, cytotoxics or immunomodulators) is therefore expected to provide advantage over conventional approaches that focus on drug delivery via the blood. Pharmacokinetically, promotion of drug transport into the lymph may also reduce hepatic first pass metabolism thereby enhancing

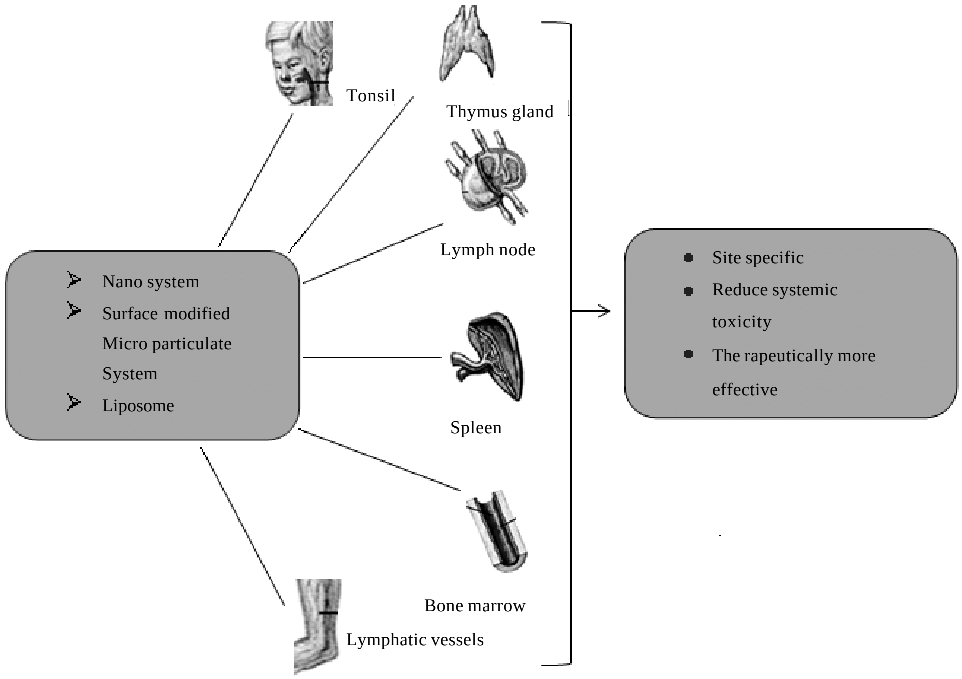

Fig. 2: Different lymphatic targeting areas

oral bioavailability (Trevaskis *et al*., 2008). Main drug targeting area of lymphatic system peripheral lymph node, lymph vessels, spleen and the thymus gland, bone marrow (Brinkmann and Baumruker, 2006). Different lymphatic targeting areas are summarised in Fig. 2.

PHYSICOCHEMICAL ASPECTS OF LYMPHATIC DELIVERY

The effectiveness of colloid uptake into the lymphatic system is affected by the physicochemical characteristics of the colloid. The rate of particulate uptake from an interstitial injection site is dictated by its rate of diffusion through the interstitium; this being dependent upon the physiological state of the interstitium, the anatomical site of injection and the physicochemical properties of the particle. These properties include size, number of particles, surface charge, molecular weight and colloid hydrophobicity. Alteration of the physicochemical properties a particle is possible by adsorption to the particle surface of a group of hydrophilic polymers, the poloxamers and poloxamines. These have been used in attempts to modify the bio distribution of particles *in vivo*, in particular with respect to the avoidance of the reticuloendothelial system (RES) following intravenous administration. Alteration of the particle surface may also occur *in vivo*, by the process of opsonisation. On exposure to blood, particulate materials become coated with plasma or serum components. Particles of differing surface characteristics attract different arrays of serum opsonins and dysopsonins, the content and conformation of which may account for the different pattern in the rate and site of particle clearance (Hawley *et al*., 1995). Different physicochemical parameters and their effect on lymphatic system have been summarised in Table 1.

Table 1: Various physicochemical parameters and their effect on lymphatic system

Name of parameter	Effect on lymphatic delivery	References
Colloid size	• Larger particles with diameters up to a few tens of nanometres will be absorbed into the lymph capillaries	Bergqvist *et al*. (1984)
	• Particles over a few hundred nanometres will be trapped in the interstitial space for a long time	O'Hagan *et al*. (1992)
	• In case of intraperitoneally administration size become less important for lymphatic drainage	
	• The only barrier to uptake from the peritoneal cavity into the lymphatics is the size limit of the open junctions of the initial lymphatic wall	Bettendorf (1979)
Concentration and volume	• Increasing the concentration of nanospheres in the injection volume which was kept constant, resulted in slower drainage from the, injection site leading to a correspondingly lower lymphatic uptake	Hawley *et al*. (1995)
	• The effect of injection volume has been studied following i.m. injection of oily vehicles to the rat. Result indicates that increasing the volume of sesame oil in these investigations was shown to accelerate oil transport into the lymphatic system	Hashida *et al*. (1977)
Surface charge	• The drainage of negatively charged liposomes has been shown to be faster than that for positive liposomes after i.p. administration	Hirano *et al*. (1985) Hawley *et al*. (1995)
	• Order of liposome localisation in the lymph nodes was negative > positive > neutral	Kaur *et al*. (2008)
Molecular weight	• There is a linear relationship between the molecular weight of macromolecules and the proportion of the dose absorbed by the lymphatics draining an S.C. injection site	Hawley *et al*. (1995)
	• Compounds with MW <1000 are hardly absorbed by the lymphatic vessels, gaining access to the blood capillaries whereas molecules with MW >16000 are absorbed mainly by the lymphatics	
	• When targeting colloids to the lymphatic system, the effect of molecular weight becomes negligible, as the molecular weight of a colloidal carrier is unlikely to be under 1000 Da	
Hydrophobicity	• The hydrophobicity of a colloid may be the major determinant of the phagocytic response and hence lymphatic uptake	Hawley *et al*. (1995)
	• The phagocytosis of hydrophobic polystyrene nanospheres was shown to be drastically reduced by the adsorption of hydrophilic block co-polymers prior to i.v. administration	
	• Poloxamine 904 caused increased lymph node sequestration of the microspheres whereas poloxamine 908 caused an increase in circulatory levels of the microspheres	

STRATEGIES FOR SURFACE ENGINEERING/MODIFICATION

Various strategies are available for lymphatic targeting. Literature suggests that drug access to the intestinal lymph is dependent on drug association with developing lipoproteins in the enterocyte. Enterocytes, lipid source, are essential to drive lipoprotein assembly is a main point to enhance lymphatic drug transport. Briefly, Fatty Acids (FA) with chain lengths of 14 or greater are easily transported by lymphatic as systemic circulation via the intestinal lymph and left absorbed via the portal vein blood. While shorter chain FA, highly water soluble, are primarily absorbed via the portal blood. Long chain FA and triglycerides (long chain FA) effectively support lymphatic drug transportation than their medium and short chain counterparts. The degree of unsaturation of administered FA also influences the extent of lymphatic lipid and drug transport (Trevaskis *et al*., 2008). Prodrug strategies also developed for lymphatic delivery of many anti-HIV and anti-cancer drugs (Bibby *et al*., 1996; Lalanne *et al*., 2007). Surface engineering technique is a new strategy for effective lymphatic drugs delivery. The influence of surface modification is as follows:

Surface modification with polyethylene glycol (PEG): Lymphatic absorption may enhance if the surface of liposome is coated with sterically stabilizing, hydrophilic layer that reduce no specific interaction of particle with the interstitial surrounding and inhibit the formation of particle structure too large. Steric stabilization can be done with PEG coating of liposome surface. This liposome would not uptake by macrophages. So PEG coating have negative effect on lymph node uptake (Oussoren and Storm, 2001).

Surface modification with ligands: It was shown that liposomes coated with non-specific human antibodies as ligand showed greater lymphatic absorption and lymph node uptake compared to uncoated liposomes at subcutaneous site. Similar results were obtained when ligand was saccharide. Saccharide modified liposomes showed enhanced absorption from the injection site and enhanced lymph node uptake compared to uncoated liposomes. Recent study with liposomes bearing Fab9 fragments (immuno-liposomes) directed against the HLA-DR surface marker which is expressed on monocytes/macro-phages and activated CD41 T-lymphocytes. That liposome was s.c. injected into the upper back of mice. The s.c. administration of anti-HLA-DR immune liposomes resulted in an up to 3-fold higher accumulation in regional lymph nodes as compared to conventional liposome (Oussoren and Storm, 2001).

Surface modification with biotin: The new subcutaneous delivery system comprises of biotin-coated liposomes, showed greater lymphatic uptake when used in combination with avidin injection to adjacent site. Lymph node uptake rose up to 14% of the injected dose with biotin liposome followed by avidin whereas biotin-liposomes without the avidin showed about 2% uptake of the injected dose. The avidin caused the aggregation of biodin coated liposome which gets entrapped during the encounter lymph node (Oussoren and Storm, 2001). Different ligand/chemicals used for lymphatic targeting are shown in Table 2.

DIFFERENT SURFACE MODIFICATION TECHNIQUES

These are the techniques for surface modification:

- Fabrication of polymeric micro particles for drug delivery (Li *et al*., 2009)
    - By soft lithography (Guan *et al*., 2006)
    - By the double emulsion method (Yang and Hsu, 2008)
    - By solvent evaporation method (Yang and Hsu, 2008)
    - By emulsification-crosslinking method (Li *et al*., 2009)
- Covalent conjugation (Kasturi *et al*., 2005)
- Encapsulation (Yuan *et al*., 2008)
- Electrostatic surface modifications (Shmueli *et al*., 2010)
- Surface coating of particles by nanospray process (Oljaca *et al*., 2005)
- Wet chemical method (Yoo *et al*., 2009)
- Surface graft polymerization (Yoo *et al*., 2009)
- Co-electro spinning (Yoo *et al*., 2009)
- Surface modification with layer-by-layer technique (Shenoy and Sukhorukov, 2004; Lu and Chen, 2004)

Table 2: Different ligand/chemicals used for lymphatic targeting

Ligands/chemicals	Delivery system	Target site	Application	References
Folate	Folate-PEG-CKK$_2$-DTPA carrier	Lymphatic metastasized tumor	Lymphatic metastasized tumor imaging diagnosis and targeting therapy.	Gu *et al*. (2010)
Lectin	Nanoparticles	Metastatic spread and growth of tumor cell	Anticancer drugs	Sinha *et al*. (2006)
L-selectin	Microparticles	Active targeting of peripheral lymph nodes	Doppler ultrasonography contrast agent.	Hauff *et al*. (2004)
PEG	Dendrimers, liposome	Lymph	Vaccine delivery	Kaminskas *et al*. (2009)
Hyaluronan	---	Lymphatic system	-----	Drobnik (1991)
Mannose	Liposome	Spleen, lymph nodes	Antiviral and anticancer drug delivery	Kaur *et al*. (2008)
β-cyclodextrin	-----	Intestinal lymphatics	Antitumor chemotherapy	Kaji *et al*. (1985)
Alginate/chitosan	Microparticles	Payer's patch	Tamoxifen, anticancer drug	Coppi and Iannuccelli (2009)
Negatively charged albumins	Microparticles	Lymph nodes and lymphatic system	Antiviral drug	Swart *et al*. (1999)
N-isopropylacrylamide/ methacrylic acid (MAA)	Nanoparticles	Thoracic lymph nodes	Chemotherapeutic agent	Liu *et al*. (2006)
Poly (lactide-co-glycolide),	Microparticles	Thoracic lymph nodes	Chemotherapeutic agent	Liu *et al*. (2006)
Block co-polymer of poloxamine and poloxamer.	Nanospheres	Regional lymph nodes		Moghimi *et al*. (1994)
Lyp-1	Nanoparticles	Targeted to lymphatic vessels and also in tumor cells within hypoxic area	Anti tumor	Luo *et al*. (2010)

Direct conjugation of ligands to PLGA micro particles has also been demonstrated to be feasible and successful in particle-targeting strategies (Mohamed and Walle, 2008). Li *et al*. (2009) studied the starch-based micro particles by water in water (W/W) emulsification crosslinking method (Li *et al*., 2009).

Partial surface hydrolysis of biodegradable aliphatic polyester films and scaffolds under acidic or basic condition has been widely used to modify the surface wettability property or to create new functionalities. This is based on the random chemical scission of ester linkages on the polymer backbones located on the very surface, resulting in the surface generation of carboxylic and hydroxyl groups from degraded, yet water insoluble polymer fragments. Surface graft polymerization has been introduced not only to confer surface hydrophilicity but also to introduce multi-functional groups on the surface for covalent immobilization of bioactive molecules for the purpose of enhanced cell adhesion, proliferation and differentiation. The surface graft polymerization is often initiated with plasma and UV radiation treatment to generate free radicals for the polymerization. While the aforementioned surface modification methods are intended to be used for prefabricated electro spun nanofibers, nanoparticles and functional polymer segments can be directly exposed on the surface by co-electro spinning with bulk polymers (Yoo *et al*., 2009).

DRUG DELIVERY SYSTEM CRITEIA FOR LYMPH TARGETING

Targeted delivery of drugs can be achieved utilizing carriers with a specified affinity to the target tissue. There are two approaches for the targeting, i.e. chemical modification of drugs and pharmaceutical modification. In the case of the chemical approaches representing so-called prodrugs, the drug has to possess a suitable functional group in its molecular structure and the method for synthesizing has to be individually developed for each drug substance. On the contrary, the pharmaceutical approach utilizing particulate carriers has such advantages that the technology, once achieved, is principally applicable to any drug and the process is comparatively easy. Emulsions and liposomes with their modifications are probably well known particulate carriers with comparatively long histories of research (Balamuralidhara *et al.*, 2011). Colloidosomes are selectively permeable to particles of various size which could be used for the controlled and sustained release applications (Swarnlata, 2010; Saraf *et al.*, 2011). Recently, various types of nanoparticles have been investigated and designed in seeking alternative carriers (Saraf, 2009). Most of those carriers accumulate to the target site during continuous systemic circulation to deliver the drug substance thereon, so-called 'passive targeting', the behaviour of which depends highly upon the physicochemical characteristics. However, much effort has been made to achieve active targeting, delivering drugs more actively to the target site utilizing specific physical forces such as magnetic force or biochemical interactions (such as receptor-ligands or antigen-antibody interactions). Different barriers to drug targeting and the role of nanosystems in overcoming these barriers have been shown in Fig. 3.

This section summarizes recent study on the lymphatic targeting, utilizing each particulate carrier.

Emulsions: Preferential lymphatic transport of drugs has been demonstrated following injection of W/O or O/W emulsions via the intraperitoneal and intramuscular routes. It was reported that selective uptake after injection into the regional lymphatics occurred in the order of O/W, W/O and aqueous solution. Colloidal system holds excellent potential as a lymphotropic carrier system. (Saraf *et al.*, 2011). More recently, an emulsion formulation consisting of an anticancer drug, Pirarubicin and Lipiodol was developed to treat gastric cancer and metastatic lymph nodes. After endoscopic injection of the Pirarubicin-Lipiodol emulsion, the drug was retained over 7 days at the injection site and in the regional lymph node (Vasir *et al.*, 2005).

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. The studies suggested that liposome-entrapped compounds were selectively transported into lymphatic tissue following intraperitoneal administration, intramuscular or subcutaneous injection. The effect of liposome size was evaluated by intraperitoneal administration of liposomes with 0.72-0.048 mm in diameter and having identical compositions. Liposome size significantly altered both fractions of lymphatically absorbed drug retained in lymph nodes and 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 un retarded 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. 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. 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

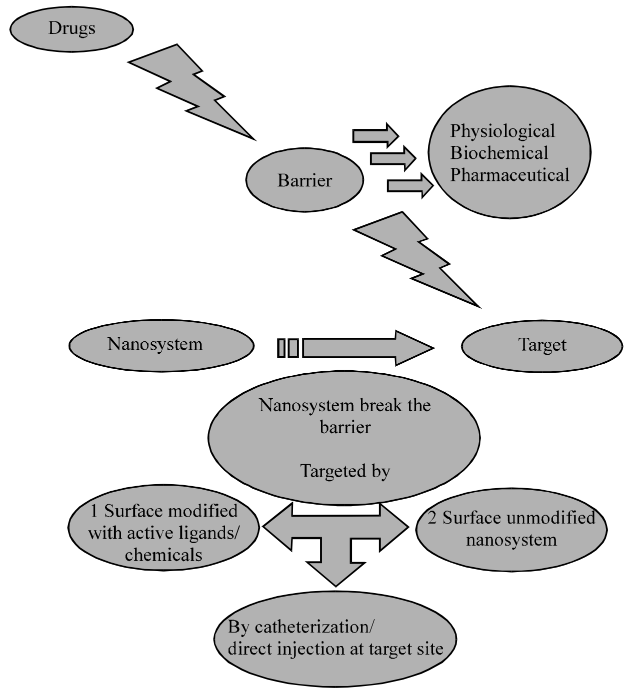

Fig. 3: Modified novel nanosystems targeting lymphatic system

been suggested that phagocytosis by macrophages is one of the major mechanisms of uptake of colloidal particles in lymph nodes. 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. To enhance targeting ability, various attempts have been made so far, including immunoliposome, PEGylated liposome and galactosylated liposome. The endoscopic gastric sub mucosal injection of liposomal adriamycin provided an enhanced lymph node targeting delivery to considerably higher levels than intravenous free adriamycin in patients with gastric cancer. As another example, a pilot study of liposomal mitoxantron for breast cancer was reported. Lymphatic targeting is also useful for diagnostic purposes. A case study is reported using blue violet entrapped in liposomes to localize lymph nodes before surgery. The liposomal structure highly stabilized by cross-linking of lipid bilayer allows the oral administration of those carriers to achieve more efficient uptake from Payer's patch. Lalanne *et al.* (2007) developed a liposomal formulation of a glycerolipidic prodrug for lymphatic delivery of didanosine via oral route in order to improve its bioavailability. Kaur *et al.* (2008) investigated the lymphatic targeting of zidovudine using surface engineered liposomes.

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 poly alkyl cyano acrylate nanoparticles and their therapeutic applications has been conducted by the research groups of Puisieux and Couvreur. 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 tumours that metastasize in the peritoneal cavity or via lymphatic pathways. They showed that uptake via Payer's patches or isolated lymphoid follicles of insulin-loaded polyisobutylcyanoacrylate nanocapsule occurred after oral administration, suggesting the possibility of per oral peptide delivery. 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 and the use of polyethylene glycols. 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). Lipid-based nanospheres should be alternative colloidal carrier systems for lymphatic targeting (Rawat and Swarnlata, 2008). The Solid Lipid Nanoparticles (SLN) were developed and evaluated for the lymphatic uptake for oral lymphatic delivery (Paliwal *et al*., 2009). As other nano-sized drug carriers, LyP-1-conjugated nanoparticles for targeting drug delivery to lymphatic metastatic tumours (Luo *et al*., 2010). Shin *et al*. (2010) prepare and evaluated of tacrolimus loaded nanoparticles for lymphatic delivery.

Nanocapsules: A nanocapsule is an ultrafine particle with a diameter of less than 1 mm with a surface coating of a polymeric substance. This is somehow different in its structural features and concept from conventional colloidal particles in emulsions which have surfaces stabilized by the adsorption of some surfactants or phospholipids. Further, nanocapsules consist of an oily core incorporating drug substances and an outer coating layer with an appropriate polymeric substance. The diameter of the particle usually ranges from tens to hundreds of nanometres. Vegetable oils, such as soybean oil, or some semi synthesized triglycerides with medium-and long chain fatty acids, Miglyol® or Panasate®, are best used for the core vehicle. Biodegradable polymers, such as polyalkylcyanoacrylates and poly-lactides have been utilized for the polymeric substance of the interfacial coating layer. Since, the surface characteristics can be modified by selecting a suitable coated polymer, nanocapsules have attracted much attention as a new type of colloidal drug carrier. Rad developed panretin-loaded nanocapsules organized by interfacial deposition of polymer (poly-ε-caprolactone) by means of sunflower seed oil (Rad, 2010). Nanocapsules may have the potential to deliver drugs to the lymph node through tissue spaces by local administration (Vasir *et al*., 2005).

CONCLUSION WITH FUTURE PROSPECTS

Various surface engineering approaches have been adopted to modify the microparticulate systems in order to enhance the delivery potential of drugs to the lymphatic system. Review of the current status of surface engineered lymphatic drug delivery research revealed that even though no carrier have yet been introduced in to clinical application, an abundance of accomplishments have been made in this field for the past two decades. The purposes of research were to provide a surface engineered lymphotropic system with an acceptable quality for clinical use and to establish a preparation method applicable for industrial production. This review will provide a platform for researchers working in this area of treating abnormalities related to lymphatic system with new approach of surface modification of various novel nanosystems. Surface engineered lymphotropic system may be an effective carrier for anti-HIV, anticancer, immunosuppressant in case of autoimmuno diseases and oral vaccine in near future.

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