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Novel Drug Carriers to Target Lymphatic System - A Review

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ABSTRACT

In the body, there is a system which is responsible for the specific resistance and in some aspects; non specific resistance is the lymphatic system which maintains homeostatic balance. This system closely allied with all the systems. Lymphatic system consist fluid called, lymph. It assists in circulating body fluids and helps in defend the body against disease causing agents. B cells, T cells and antibodies protect all body systems from attack by harmful foreign invaders (pathogens), foreign cells, and cancer cells. Major functions of lymphatic system are draining excess interstitial fluid, transport dietary lipids and carring out immune responses. Now a days there is a high risk to immune system because of the diseases or due to disorders. In recent innovations, nano technology plays a major role and there are the different drug carriers are used to avoid the major damage to immune system. This review explains about the drug carriers to target lymphatic system to release the drug at a specific part in the lymphatic organs, tissue or lymph in different disease conditions.

Keywords: *lymphatic system, Nanotechnology, drug carriers, drug targeting, drug release mechanism*

Description of the lymphatic system:

The lymphatic system is a network of tissues and organs that primarily consists of lymph vessels, lymph nodes and lymph. The tonsils, adenoids, spleen and thymus are all part of the lymphatic system. There are 600 to 700 lymph nodes in the human body that filter the lymph before it returns to the circulatory system.[1]

The **spleen**, which is largest lymphatic organ, is located on the left side of the body just above the kidney. Humans can live without a spleen, although people who have lost their spleen to disease or injury are more prone to infections. The **thymus**, which stores immature lymphocytes and prepares them to become active T cells, is located in the chest just above the heart. [2]

Tonsils are large clusters of lymphatic cells found in the pharynx. When bacteria are recognized in the lymph fluid, the lymph nodes make more infection-fighting white blood cells, which can cause swelling. The swollen nodes can sometimes be felt in the neck, underarms and groin.[3]

Unlike blood, which flows throughout the body in a continue loop, lymph flows in only one direction upward toward the neck within its own system. It flows into the venous blood stream through the subclavien veins, which are located on either sides of the neck near the collarbones. Plasma leaves the cells once it has delivered its nutrients and removed debris. Most of this fluid returns to the venous circulation through the venules and continues as venous blood. The remainder becomes lymph. Lymph leaves the tissue and enters the lymphatic system through specialized lymphatic capillaries. About three-quarters of these capillaries are superficial capillaries that are located near the surface of the skin. There are also deep lymphatic capillaries that surround most of the body's organs. [4] There are two drainage areas that make up the lymphatic system. The right drainage

area handles the right arm and chest. The left drainage area clears all of the other areas of the body, including legs, the lower trunk, the upper left portion of the chest, and the left arm.[5]

INTRODUCTION: DRUG DELIVERY TO LYMPHATIC SYSTEM

The development of carrier systems for the targeted delivery of agents to lymph nodes has a wide variety of potential medical applications, including the treatment of viral and bacterial infections, prevention of tumor metastasis, and as a delivery vehicle for vaccine antigens. Colloidal particles, which are injected either s.c., i.m., or i.p., are cleared through the lymphatic system and accumulate to varying degrees in the lymph nodes. [6]

Properties of particulate drug carriers in relation to lymph node targeting

There have been some fundamental studies of lymphatic targeting via routes other than intra tumoural administration. Liposomes , polymer particles, and drug polymer conjugates were administered by subcutaneous (s.c.), intravenous (i.v.), or intra-peritoneal (i.p.) injection.[7] It has been found that particles with nanometer diameters are required for significant lymphatic distribution, while relatively larger particles (e.g. ~700nm) are preferentially retained in the lymph nodes s.c. administration requires smaller particles than intra-peritoneal injection, more hydrophobic particles display higher lymphatic distribution and surface modification of particles alters their lymph node distribution.

Surface charge may be another important factor. The order of liposome localization in the lymph nodes was negative > positive >neutral. It is conceivable that particle size, hydrophobicity, and surface charge play important roles in lymphatic targeting. However, how these properties would influence lymphatic uptake of the carriers through the pleural lymphatic system needs to be investigated.[8]

Particulate drug delivery systems for lymphatic targeting

Lymphatic selectivity is most effectively provided by direct injection of drugs into lymphatic vessels, but technical difficulties have limited its practical employment. Delivering anticancer agents to regional lymph nodes has been attempted in the treatment of ovarian cancer, esophageal cancer, and breast cancer. In these studies, carbon or silica particles were used as drug carriers and injected subcutaneously or intratumourally. Both experimental and early clinical trials revealed considerable drug accumulation in lymph nodes and reduced cytotoxic drug levels in the plasma. It is generally accepted that lymphatic uptake of intravenously (i.v.) administered colloidal particulate is unlikely since colloids cannot undergo transcapillary passage because of their larger size. After i.v administration, they are mainly taken up by macrophages in the liver and the spleen. Targeting to the lymph nodes for drug delivery purposes has been attempted with various drug carrier systems.[9]

Nanotechnology mediated targeted drug delivery systems

Drug delivery systems are defined as supramolecular assemblies incorporating agents intended to treat a disease. They are intended to overcome the shortcomings of the conventional drugs, such as unfavorable pharmacokinetics, poor solubility, instability, high toxicity, drug resistance and low cellular uptake. [10]

Nanotechnology

The use of nanotechnology for drug delivery rapidly produced commercially available products and the term nanomedicine emerged. Nanomedicine is the application of nanometer scale materials in an innovative way to develop new approaches and therapies. At this scale, materials display different physicochemical properties due to their small size, surface structure and high surface area. These properties allow nanoparticulate systems to overcome current limitations of conventional formulation as they facilitate the intracellular uptake to specific cellular targets. Thus, nanotechnology has been adopted in several fields such as drug/gene delivery, imaging and diagnostics Liposomes and emulsions dominated the drug delivery field for some period. With the renewed interest in nanotechnology, new nano-sized formulations and nanomaterials have been developed. These new materials include polymeric nanoparticles, solid lipid nanoparticles, liposomes, nanoemulsions, cyclodextrins and dendrimers etc. [11]

CARRIERS FOR TARGETED DRUG DELIVERY TO LYMPHATIC SYSTEM

The success of the targeting strategy of the immune system was the presence of both unique receptors and unique markers molecules on the surface of the cells. [12]

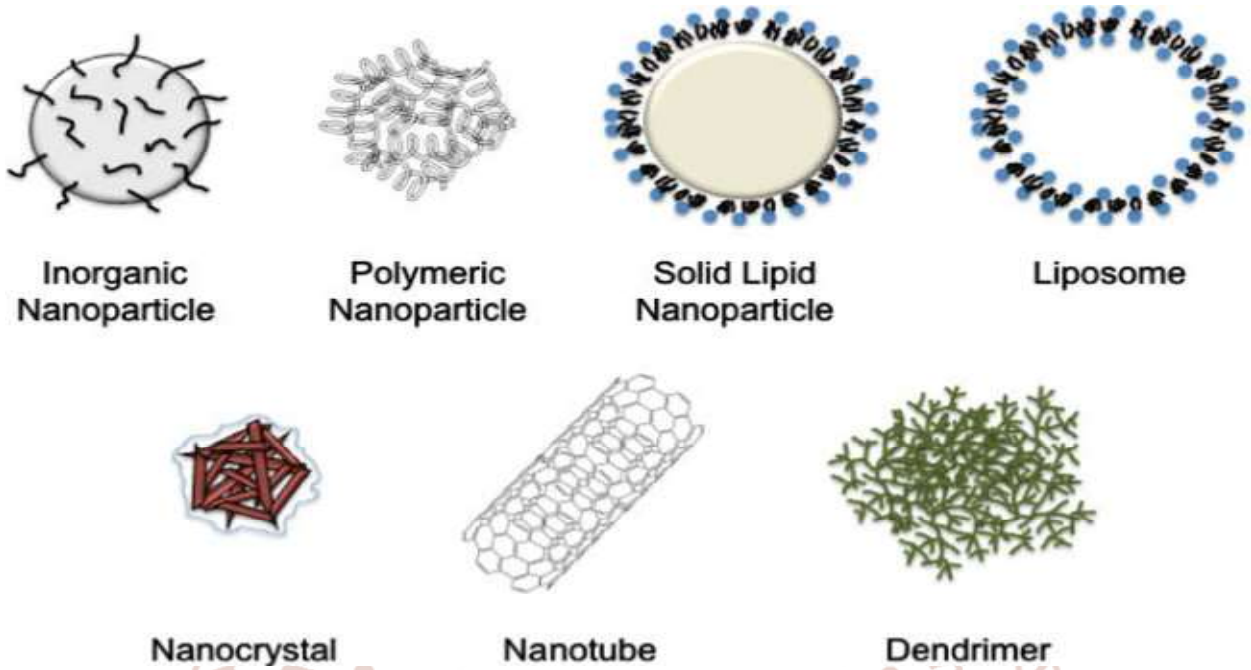


Figure: 1 Carriers for Targeted Drug Delivery

A.POLYMERIC NANOPARTICLES:

Nanoparticles are solid, colloidal particles consisting of macromolecular substances varying in size from 10 to 1000 nanometers. A drug can be dissolved, entrapped, adsorbed, attached or encapsulated into a nano-particle. [13] Depending on the method of preparation, nanospheres or nanocapsules can be developed with different properties and different release characteristics for the encapsulated therapeutic agent. For nearly three decades, polymeric nanoparticles have been studied extensively because of their unique and valuable physicochemical and biological properties.

Polymeric nano particles:

Polymeric nanoparticles are of diameter below 1µm. natural polymers are usually widely used, because of chances of variation in purity, requirement of crosslinking and chances of denaturation of drug. [14]

Most widely used polymers:

Natural proteins or poly saccharides**,** synthetic poly lactic acid, poly glycolic acid, co-polymers: poly lactide co glycolic acid [PLGA] & poly alkyl cyano acrylates[PACA] **.**These polymers offer the advantage of sustained release of drug and avoid in repeated dosing. [15]

Eg1: Prolonged hypoglycemia is produced by PACA nano spheres entrapped with insulin and dispersed in an oily phase with a surfactant.

Polymeric drug delivery systems for lymphatic targeting

There is limited information on lymphatic targeting using polymeric drug delivery systems. Although polylactides (PLA), polyglycolides (PGA), and their copolymers (PLGA) have been developed for local delivery of chemotherapeutic agents, the primary design was for the treatment of cancerous peritonitis rather than targeting lymphatic metastasis. The greatest advantage of these degradable polymers is that they can be broken down into biologically acceptable molecules e.g. lactic or glycolic acid and water that are metabolized and removed from the body via normal metabolic pathways. [8]

B.SOLID LIPID NANOPARTICLES:

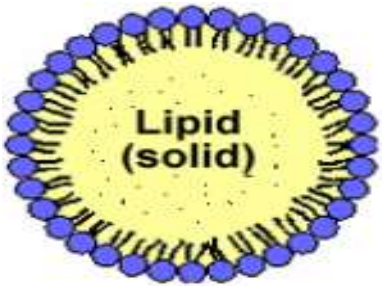


Figure: 2 Solid Lipid Nanoparticle

Solid lipid nanoparticles (SLNs) are nanocrystalline structures made of fatty acids that are solid or semisolid at room temperature. A wide variety of high melting-point lipids and methods can be used to prepare and stabilize the SLNs. [16, 17]

Figure: 3 types of Solid lipid nanoparticles

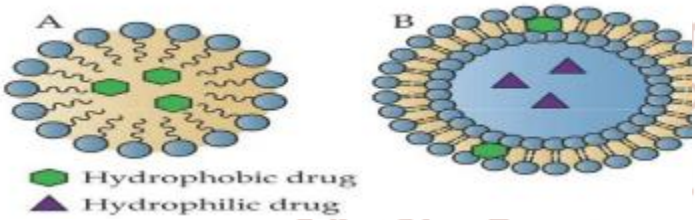


Figure: 4 mechanism of solid lipid particle

Lymphatic targeting:

The most important structural units of the gut associated with lymphoid tissue are the **peyer's patches.** These are characterized by the presence **of M cells** which helps in endocytosis, transport into intra epithelial regions, adjoin lymphoid tissue **.**Usually, nano particulates bind to apical membrane of **M cell** Followed by rapid internalized and transport to the lymphocytes**.**

The absorption of a drug via the GALT has a distinct advantage in avoiding pre systemic hepatic first pass metabolism and thereby preventing during loss. In NPS critical aspects is the loading capacity, the higher the loading the higher is the B.A. per particle absorbed. [18]

Solid lipid nanoparticles (SLN's) in lymphatic cancer therapy:

Lymphatic targeting can also provide an effective anti-cancer chemotherapy to prevent the metastasis of tumour cells by accumulating the drug in lymphnodes. [19]

DRUG RELEASE AND RELEASE KINETICS OF NPS

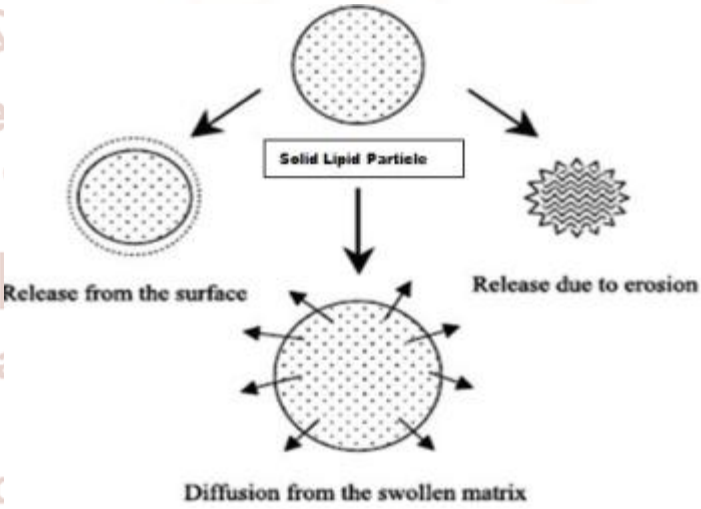


Figure:5 Drug Release And Release Kinetics

C. LIPOSOME, a hydrophilic head and a hydrophobic tail and are oriented so that the hydrophobic head groups are inside the bilayer. Being versatile, non-toxic and biocompatible lipid vesicles, have received the most attention as carriers of various drugs Among the lipid-based nanoparticular drug delivery systems potentially useful for efficacious lymphatic drug delivery, liposomes have received significant attention for its ability to enhance the permeability of drugs across the enterocyte, to stabilize drugs, and to provide the opportunity of controlled release. [20]

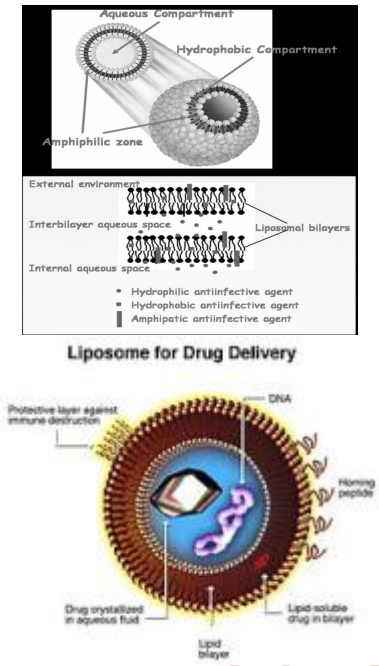


Figure: 6 Liposomes and its drug delivery

Liposomes, spontaneously forming lipid spheres, are one class of colloidal particle, which is proving to be a versatile carrier for a wide variety of i.v. administered agents, including drugs, contrast agents, biologics, and DNA Liposomes are currently under investigation as lymph node delivery vehicles when administered through an s.c. or i.m. route. Liposome delivery system may prove useful for the delivery of chemotherapeutic drugs, vaccine antigens, and biologic agents to lymph nodes.

Eg1: cefotaxime, a hydrophilic drug with poor bioavailability, was encapsulated in liposomal carriers to protect it from the effects of low pH and increase transport of the drug into the intestinal lymph as well as its systemic bioavailability

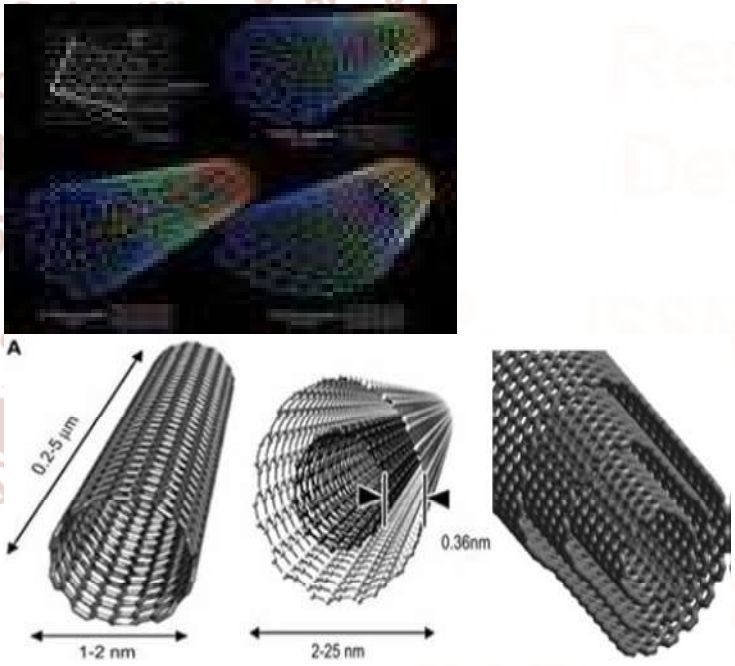
Oral bioavailability of the drug in the liposomal formulation and drug given with empty liposomes was 2.7-fold and 2.3-fold greater, respectively, than that of drug given in aqueous solution. They also reported that lymphatic localization of the drug was considerably increased compared to the other formulations. Thus, liposomes can be used as drug carriers to increase the intestinal lymphatic transport and the oral bioavailability of hydrophilic drugs with poor bioavailability. [21]

Eg2: A DNA vaccine, since DNA vaccines are unstable after oral administration, an effective method is needed to improve their stability. Then Oral delivery of liposomes with entrapped DNA vaccines was reported. Their stability studies in simulated intestinal media revealed significant differences in excreted IgA levels between mice dosed with liposome encapsulated DNA and mice dosed with naked DNA. The immunological response induced by liposomal DNA vaccines was bigger than that induced by naked DNA. [22]

PEGylated Liposomes:

Modified liposomes have been used to increase transport of drugs to the intestinal lymphatics. For example, polyethyleneglycol (PEG)-coated liposomes were developed to improve absorption of human epidermal growth factor (rhEGF), a single-chain polypeptide containing 53 amino acid residues and three disulfide bonds. [23]

D. CARBON NANOTUBES: A VERSATILE TECHNIQUE FOR DRUG DELIVERY



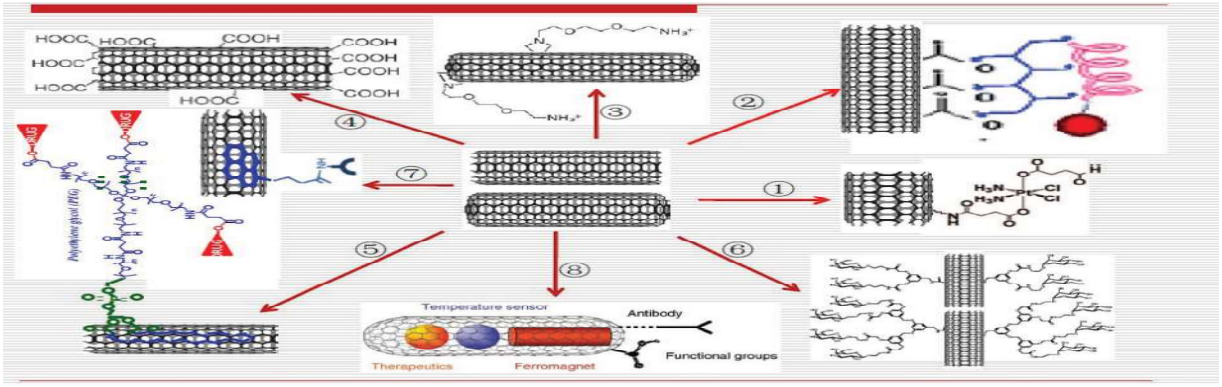


Figure: 7 Carbon Nanotubes and Its Mechanism

Mechanism of cellular uptake

CNTs are capable to penetrate into cellular membrane and active cellular constituents without causing damage to the cells; this is achieved due to their needle shape. Water soluble CNT are able to enter the cells and cellular uptake is based upon size and surface chemistry. CNT functionalized by oxidation, coated with surfactants or polymers are engulfed by cells via endocytosis path way. Due to their needle shape CNTs are capable to penetrate into the cellular membrane and pass into the cellular components without causing cell damage. Chen and coworker designed the nano injector using atomic force microscopy. In that, tip of functionalized MWCNTs were attached to the model carrier compound through disulfide linker and it was successfully transported into the cell where disulfide bond breaks that results in the release of the compound into the cell. Vertical positioning of CNTs to the cell membrane shows that uptake of CNTs was similar to nano needle which diffuses into the cell by without causing cellular damage. [24]

Lymph targeting

Lymph metasis occur in cancer which results in frequent tumor reoccurrence even after lymph dissection. In order to overcome this issue, F. Yang et al. used magnetic MWCNT which delivered gemcitabine to lymph node under the guidance of magnetic field. By using this method various chemotherapeutic agents can be delivered to lymph node. [25]

E.DENDRIMERS (POLYMERS)

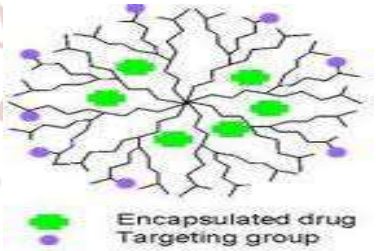


Figure: 8 Dendrimers and Its Mechanism

Dendrimers are a versatile class of regularly-branched macromolecules with unique structural and topologic features that are 2.5 – 10 nm in size. They consist of repeatedly branched polymeric macromolecules with numerous arms extending from a center, resulting in a nearly-perfect three-dimensional geometric pattern. They have a remarkable well-defined control over size (comparable size to proteins) with narrow polydispersity. Small size, narrow molecular weight distribution, and relative ease of incorporation of targeting ligands make them attractive candidates for drug delivery. [26]

Targeting dendrimers:

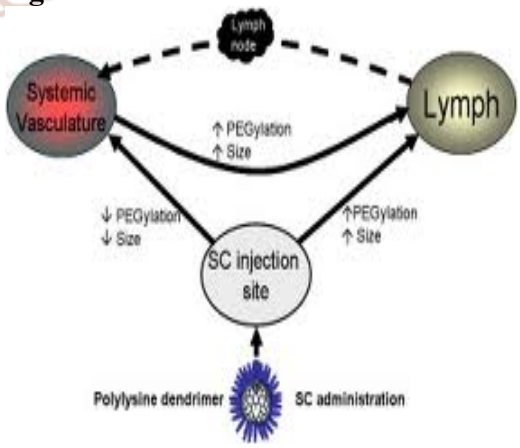


Figure: 9 targeting dendrimers to lymph

Dendrimers have been used to prepare nanoparticles i.e diameter below 50nm to study the relationship between diameter and uptake from GIT.

Eg1: Phospholipid coated poly amidoamine dendrimers entrapped with 5-flurouracil have shown to be more effective orally than free drug with increase in lymphatic uptake, indicating absorption of the dendrimer through the lymphatic route. [27]

F.MICELLES:

Micelles are colloidal structures with particle diameter 5-100nm belong to a group of association or amphiphillic colloids. [28]

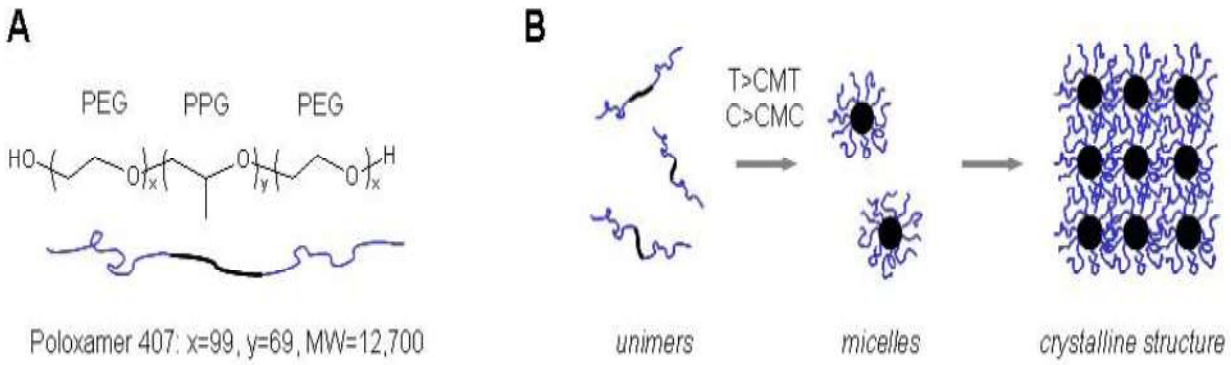


Figure: 10 (A) Poloxamer structure and (B) self-assembly

The copolymer is in unimer form at low temperature or concentration. With increasing temperature (at concentrations exceeding the CMC) self-assembly into micelles occurs. Close-packing of micelles in crystalline structures, above a concentration threshold, leads to its gel-like behavior. [29]

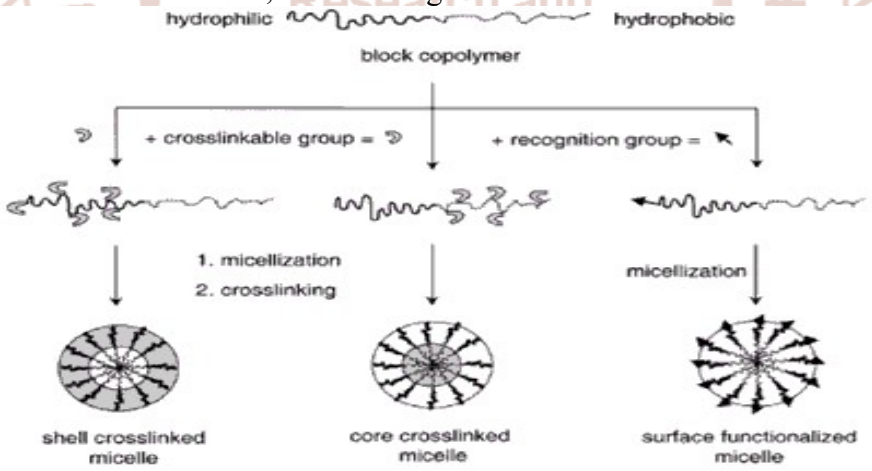


Figure: 11 types of packing of micelles

At low concentrations in an aqueous medium such amphiphilic molecules exhist separately, however as their concentrations increased aggregations take place. The concentration of monomeric amphiphilie at which micelles appears is called the critical micelle concentration. Where the amphiphiles below this concentration as unimers and above this as aggregates. [30]

Eg1: Micelles of the PEG-poly lactide copolymer surface modified with galactose units can interact with lectins. Letins receptors are present on HIV viral reservoirs, such as T-lymphocytes and macrophages. Thus these copolymers can be used as an approach for targeting reservoirs. [31]

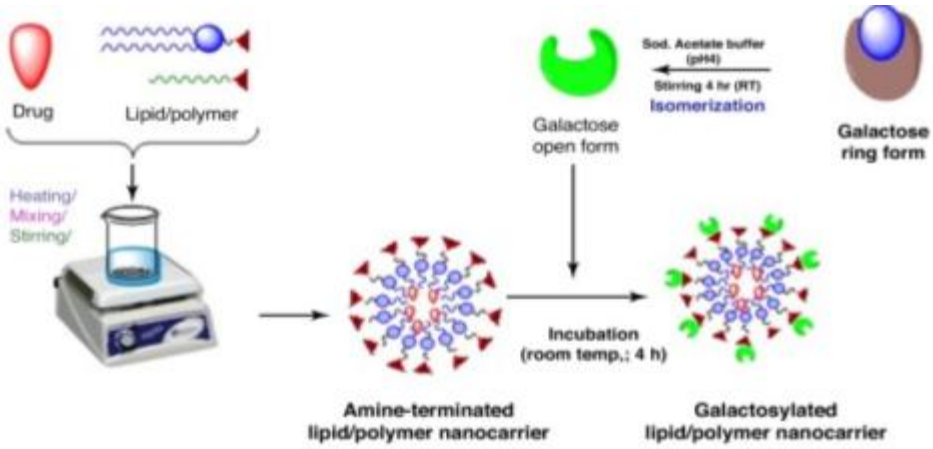


Figure: 12 Micelles of the PEG-poly lactide copolymer with galactose units

G.EMULSIONS has been considered as carriers and has been investigated as lymphatic targeting systems. The composition of the emulsion has mainly been considered with little focus on the size of the emulsion droplets, which has already been shown to be a major factor in lymphatic targeting. Other, non-lipid delivery systems have also been used, which are mainly polymeric in nature.

Emulsions are heterogeneous delivery systems generally consisting of a dispersed phase and a continuous phase with the interface between them. In oil-in-water emulsions, the oil is dispersed as droplets within an aqueous phase. Water-in-oil emulsions are also possible. Emulsions with droplet sizes <100 nm are called micro emulsions and are thermo dynamically stable systems. Microemulsions are systems consisting of water, oil, surfactants and co-surfactants, and they have the capacity to solubilize both water-soluble and oil-soluble drugs. Emulsions and micro emulsions can be used as carriers for drugs with poor water solubility, as sustained-release systems and as site-specific drug delivery vehicles by binding ligands for various cell-receptors to the particle surface. Administration of a poorly water-soluble drug as an emulsion may improve bioavailability by eliminating a slow dissolution step as a barrier to drug absorption, by enhancing intestinal lymphatic drug transport, or by a combination of both processes. Other potential mechanisms by which emulsions may enhance drug absorption include effects on gastrointestinal membrane permeability, transit time or on the metabolism of the drug. [32]

H. IMMUNOCONJUGATES

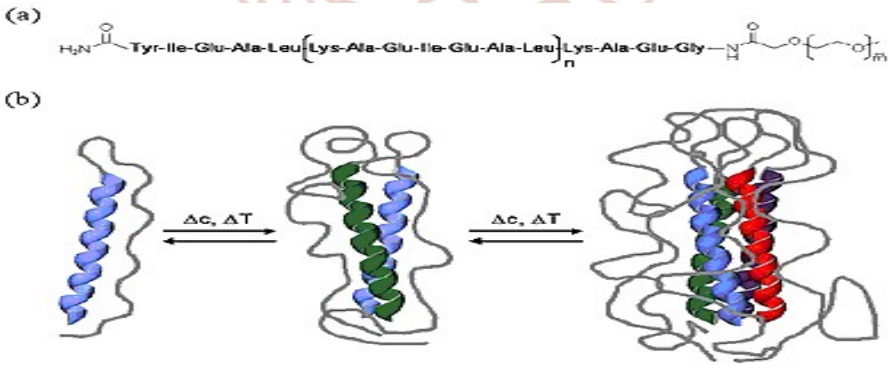


Figure: 13 Immunoconjugates

Antibody drug-conjugates or immunoconjugates are recombinant antibodies covalently bound through a linker to a drug. The idea behind this technology is to target potent drugs to the specific site by using the specificity of monoclonal antibodies (mAb) thus avoiding non- targeted organs toxicity. These systems

can be applied to encapsulate multiple drugs while protecting from the external environment and exert a controlled release. [33]

Monoclonal antibodies (MABs): Research in immunology and cell biology has resulted in the commercialization of naturally produced active drug substances for therapy. Until recently many of these active drug substances were only produced in-vivo in the body. Many naturally produced substances are complex molecules and have potential to form drug conjugates which can be selectively taken up by target cells and digested by lysosomal enzymes. In kidney transplant, a T -cells MAB against CD" a protein of cytotoxic that causes rejection reaction is very useful in suppressing rejection and allowing the transplant to function. This conjugate is reported as OKT3. [34]

Eg:Rituximab (Rituxan®):This is an antibody that attaches to a substance called CD20 found on some types of lymphoma cells. [35]

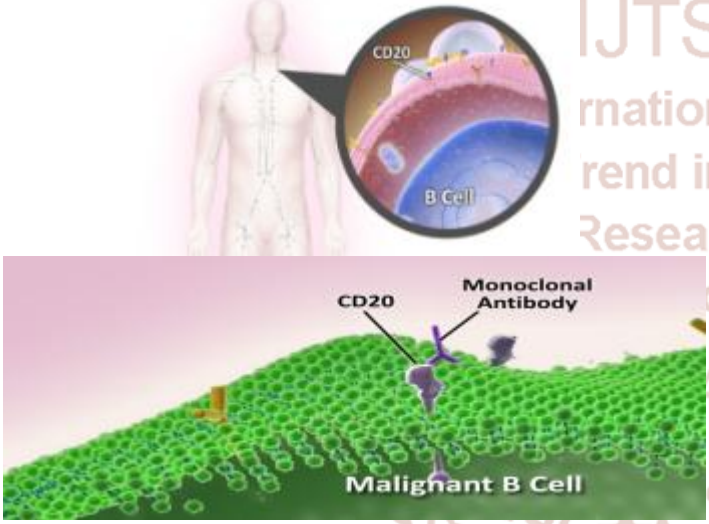


Figure: 14 Drug Targeting To Monoclonal Antibodies Of Lymphoma Cells

I.PRODRUG (S): Prodrugs have also been called latentiated drugs, bioreversible derivatives and congeners. Usually prodrug implies a covalent link between a drug and chemical moiety, although some times this term is used to characterize some salt of active drug. These approaches are not only very useful in decreasing side effects but also increase/decrease solubility as required, lipophilicity, mask taste and enhance bioavailability. Prodrug technology is generally considered as a useful technique in improving corneal permeability of ophthalmic drugs. [36]

Prodrugs designed for enhanced lymphatic delivery

The lipophilicity of drugs can also be increased by attaching lipid molecules. Various lipid molecules such as a fatty acids, monoglycerides, diglycerides, or phosphoglycerides can be covalently bound to drugs to produce prodrugs. This approach is based on the fact that high lipophilicityis required for transport into intestinal lymph. An early attempt to increase the lipophilicity of drugs was a synthesis of simple esters by condensation with long-chain fatty acids.

Eg1: Testosterone, the absolute bioavailability of unmodified testosterone was approximately 4 % due to first-pass hepatic degradation. An absolute bioavailability of about 7 % was achieved by attaching a lipid molecule to the hormone, producing a lipophilic ester prodrug.

Eg2: Epitiostanol, an anti-tumor agent, was modified by attaching 17-methoxycyclopentane ether to the drug producing an ether derivative of epitiostanol. The modified drug had superior bioavailability when compared with native testosterone. [37]

Conlusion:

With this I conclude that, lymphatic system is major system which helps from the different diseases and maintain homeostasis in the body. But recently immune system is also effected with so many disases and disorders. For the treatment of lymphatic system diseases , to avoid the firstpass metabolism and to improve the bio availability of the potent drugs is majorly done by nano carriers which are used to drug targeting. This review explains about polymeric nanoparticles, solid lipid nano particles, liposomes, carbon nanotubes, dendrimers, micelles, emulsions, immunoconjugates and prodrugs with their lymphatic targeting. Recently, cyclodextrins, metal nanoparticles, quantum dots and nano crystals are also developing for lymphatic targeting is initiated.

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