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Ruminative Announcement on Nanoparticles and Mononuclear Phagocytic System

J. Balasubramanian[1*], T. Sravanthi[2], V. Sujitha[2]

[1]*Aeon Formulation Pvt. Ltd, Ramapuram, Chennai- 600 089, Tamil Nadu, India*
[2]*Annamacharya College of Pharmacy, Department of Pharmaceutical Analysis & Quality Assurance, Department of Pharmaceutical & Drug Regulatory Affairs, Rajampet- 516 126, Kadapa (Dist) Andhra Pradesh, India*

ABSTRACT

The aim of the present review provides the relationship between therapeutic nanoparticles and mononuclear phagocytic system. Reticuloendothelial system (RES) represents a group of cells having the ability to take up and sequester inert particles and vital dyes. This includes macrophages and macrophage precursors, specialized endothelial cell lining the sinusoids of the liver, spleen and bone marrow, and the reticular cell of the lymphatic tissue (macrophages) and of the bone morrow (fibroblast). Nanoparticles are rapidly sequestered and retained by the organs comprising of the reticuloendothelial system (RES), mainly the liver, spleen and the bone marrow. Thus, targeting of the nanoparticles to the reticuloendothelial system (RES) is much simpler than to any other organ. In the liver, the particles are mainly retained by the scavenging periportal and midzonal Kupffer cells, while the hepatocytes and liver endothelial cells may play a secondary role under special pathophysiological conditions or for special physic- chemical characteristics of particles. The clearance of conventional nanoparticles has been proposed to occur by uptake of the nanoparticles by the reticuloendothelial system (RES). The mononuclear phagocytic system uptake of nanoparticles results in their rapid removal from the blood and accumulation in tissues involved in the RES, such as the liver and spleen. Uptake by the RES usually results in irreversible sequestering of the encapsulated drug in the RES, were it can be degraded. In addition, the uptake of the nanoparticles by the RES may result in acute impairment of the mononuclear phagocytic system and toxicity. Sterically stabilized nanoparticles, such as STEALTH nanoparticles, prolong the duration of exposure of the encapsulated nanoparticles in the systemic circulation. The presence of the PEG coating on the outside of the nanoparticles does not prevent uptake by the reticuloendothelial system, but simply reduces the rate of uptake.

Keywords: Nanoparticles, Mononuclear Phagocytic System, Reticuloendothelial System, STEALTH nanoparticles.

INTRODUCTION

A number of new molecular entities (NMEs) selected for full- scale development based on their safety and pharmacological data suffer from undesirable physicochemical and biopharmaceutical properties, which lead to poor pharmacokinetics and distribution after *in- vivo* administration. [1]

Reticuloendothelial System, also called as macrophage system or mononuclear phagocyte system, class of cell that occur in widely separated parts of the human body and take up particular substance. These cells are part of the body's defense mechanisms. [2]

***Corresponding author: Dr. J. Balasubramanian,**
No, 54 Sidhi Vinayagar Koil Street, T- Nagar, Chennai- 600 017, Tamil Nadu, India; **Tel.:** +91-9719143848;
E-mail: hippocratesbala@gmail.com
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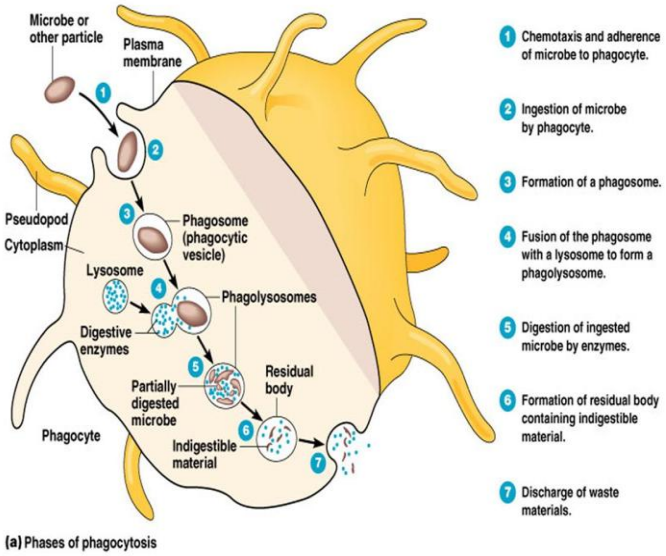

Fig. 1: General Mechanism Involved In Phagocytosis

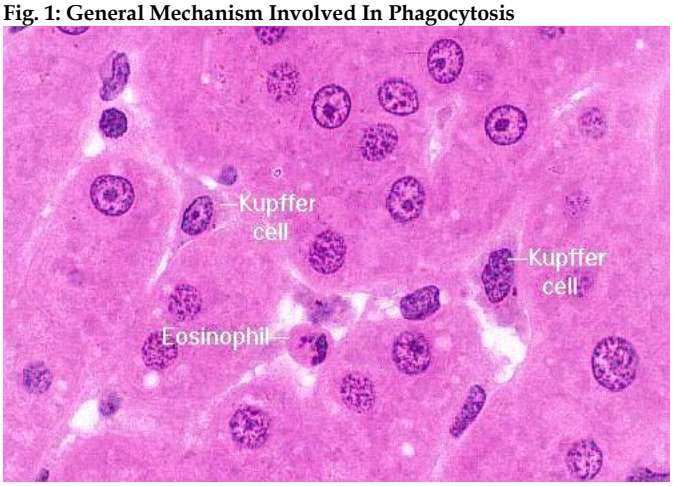

Fig. 2: Liver Kupffer Cell

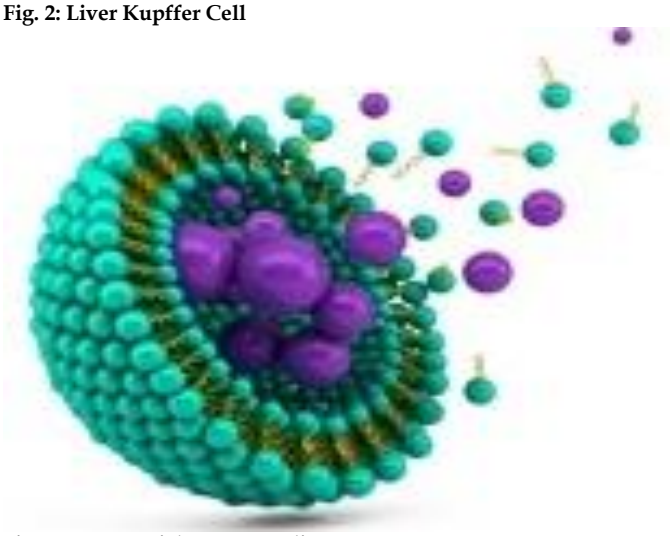

Fig. 3: Nanoparticles Drug Delivery

The RES has four major components which are Lymph nodes, spleen, Mucosa-associated lymphoid tissue (MALT) including gut-associated lymphoid tissue (GALT), bronchus-associated lymphoid tissue (BALT) and the palatine, lingual and pharyngeal tonsils. A variety of specialized fixed phagocytes including Kupffer cells (throughout the liver), Langerhans /dendritic cells (skin), dust cells (alveoli) and microglial cells (brain). [3]

Reticuloendothelial cells are phagocytic; i.e., they can over whelm and destroy bacteria, viruses, and other distant substances. They also can ingest worn-out or abnormal body cell. Reticuloendothelial cells are derived from ancestor cells in the bone marrow. These ancestors develop into monocytes, phagocytic cells that are released into the bloodstream. Some monocytes remain in the general blood circulation, but most of them enter body tissues, where they develop into much larger phagocytic cell called macrophages. The great majority of macrophages remain as stationary cells within tissue, where they filter out and wipe out foreign particles. Some of them smash away, however, and wander through the circulation and within the intercellular spaces. [2]

Nanotechnology can simply be defined as the technology at the scale of one- billionth of a meter. It is the design, characterization, synthesis and application of materials, structures, device and systems by controlling shape and size at nanometer scale.

The novel properties of nanoparticles offer the ability to interact with complex cellular functions in new ways. [4]

Tissue macrophages are distinct in emergence and name because of their various sites. For example, reticulum cells line the sinuses of the lymph nodes, spleen, and bone marrow, while histiocytes are found in many subcutaneous tissues. Microglia occurs in nervous tissue, alveolar macrophages in the air spaces of the lungs, and Kupffer cells in the liver.

A single Reticuloendothelial cell can phagocytize (engulf and destroy) microorganisms, cells, and even tiny fragments of foreign objects, such as bits of splinters and suture materials. Several movable macrophages can surround larger foreign objects and merge in to a single phagocytic cell. By their phagocytosis of foreign substances, macrophages form a significant first line of protector against damaging particles that have acquired the body's interior. The Reticuloendothelial cells also participate in body defense through immune reactions, a complex set of events targeted at a specific foreign substance. The reaction is desired by white blood cells known as lymphocytes. One class of lymphocytes (B cells) can synthesize and secrete antibodies with the help of another class of lymphocytes (T cells). T cells are also capable of other immunological reactions not involving antibody production. Macrophages often appear to be a required factor in an immune reaction. It is reputed that phagocytosis of the foreign substance by macrophages helps reveal the surface molecules (antigens) on the distant substance that stimulate lymphocyte responses. The production of antibodies, in turn, greatly stimulates the phagocytic activity of the macrophages.

A further worthy function of the Reticuloendothelial cells is the obliteration of worn-out or abnormal cells and tissues. The reticulum cells of the spleen in particular play a major role in the destruction of worn-out red blood cells and the recycling of hemoglobin, the

oxygen-carrying pigment of the red blood cells. The reticulum cells collapse old red blood cells and metabolize the hemoglobin to create hemosiderin, a pigment used to form new red blood cells.

Syndrome associated with the Reticuloendothelial system include anemia caused by extreme destruction of red blood cells by reticulum cells there are also malignant tumours related to Reticuloendothelial cells that can be either localized or extensive throughout the body; Reticulum-cell sarcoma is the most common such neoplasm and is usually located in the lymph nodes. Another condition, histiocytic medullary reticulosis, results from the diffuse proliferation of phagocytic cells. Niemann-pick and Gauche's diseases are hereditary disorders characterized by abnormal products of lipid metabolism within the reticuloendothelial cells. [2]

Particulate systems like nanoparticles have been used as a physical approach to alter and develop the direction of the drug within the tissue with respect to time (i.e. pharmacokinetics) and fruitful therapeutic effects of the drug on the body (i.e. Pharmacodynamics) of various types of drug molecules. The possible juncture between nanotechnology and the biological sciences is vast. Biological function depends heavily on units that have Nano scale dimensions, such as viruses, ribosome's, molecular motors and components of the extra cellular matrix. In addition, engineered devices at the Nano scale are small enough to interact directly with sub-cellular compartments and to probe intracellular events. They have been used *in vivo* to protect the drug entity in the systemic circulation, restrict access of the drug to the chosen sites and to deliver the drug at a controlled rate and sustained manner to the desired site of action. Various polymers have been used in the formulation of nanoparticles aiming to increase the therapeutic benefit through drug delivery research, while minimizing side effects. The purpose of these review work is to give the brief idea about various aspects of nanoparticles with their history, formulation, characterization, effect of their characteristics and their applications in delivery of drug molecules. [5]

IMMUNE RECTIONS IN LYMPH NODES

The lymph nodes play host to a series of complex cellular interactions that commonly advantage to the production of specific antibodies. These are centered on fixed macrophage populations. On exposure to a potential pathogen, such as a bacterium, the fixed macrophages engulf the bacterium by phagocytosis then digest it, preventing further bacterial replication. Pieces of the digested bacterium are presented on the surface of macrophage to circulating T-lymphocytes, which become activated and produce a cocktail of cytokines. These stimulate the B-lymphocytes to divide and produce specific antibodies against the offending bacteria. After the process described above, some noticeable physiological effects may occur. [3]

The human digestive system is fundamentally an incessant tube, which is open at both ends. Therefore, the lumen (cavity) connects directly with the adjacent environment. Along with the ingested food, barely anything can pass through the mouth into the digestive system. The digestive tract is open to the adjacent environment also at the other end, the anus.

The reticuloendothelial system since a variety of toxic materials and/or microorganisms may be compressed with ingested foods; special protective mechanisms are associated with the human digestive system. Such protective mechanisms are said to belong to the reticuloendothelial system. This term refers to the association of such mechanisms with a particular layer of epithelial cells. Lymphoid Tissues The lymphoid tissues are a primary component of the reticuloendothelial system. The lymphocyte is an important type of white blood cell that is also found in the aperture of lymphoid (or lymphatic) tissues. Lymphocytes signal other types of white blood cells to phagocytize (engulf) foreign materials found within the body.

The lymphoid tissues are chiefly important in individuals from birth until about 15 years of age. The mass of lymphoid tissue found in the body of a 12 year old is about twice the mass found in a full-grown adult. Between 6 and 15 years of age, the immune system of the blood becomes the leading protector of the body from disease. Tonsils are aggregates of lymphoid tissue found at the beginning of the pharynx. There are three pairs of tonsils. Together, they form a ring of lymphoid tissue at the experimental of the pharynx. This ring called Waldeyer's ring, absolutely surrounds the point of dispatcher to the pharynx from both the mouth (digestive entrance) and the nose and nasal chambers (respiratory entrance). In the upper recess of the pharynx is the pair of pharyngeal tonsils (commonly known as the adenoids). On either side, below the soft palate, are the palatine tonsils. These are the tonsils that one sees most frequently in small children.

The lingual tonsils are on the back of the root of the tongue. "Tonsils" of the Small Intestines Lymphoid agglomerates of variable size are found in the walls of the small intestines. In the ileum portion, in precise, these agglomerates are large enough to be easily checked and are called Peyer's patches. These might be measured "tonsils" of the small intestines. "Tonsils" of the Large Intestine At the experiential of the large intestine, at the inferior end of the cecum, is a structure known as the vermiform appendix. Since the vermiform appendix is actually a collection of lymphoid tissue, it should be measured the "tonsil" of the large intestine. Kupffer's Cells As we have seen, blood from the assimilative areas of the gut tract is collected and conveyed to the liver by the hepatic venous portal system. As this blood passes through the sinusoids (channels) of the liver, it is acted upon by cells called Kupffer's cells. These cells line the

sinusoids. Since Kupffer's cells remove injurious substances from the blood, they are considered to be part of the reticuloendothelial system.

Reticuloendothelial system lymphoid tissues are leading component of system. Lymphocyte is important type of white blood cell that is also found in interspaces of lymphoid (or lymphatic) tissues. Lymphocytes signal other types of white blood cells to phagocytize (engulf) foreign materials found within the body. Lymphoid tissue precise important in individuals from birth until about 15 years of age. Mass lymphoid tissue found in body of 12 year old is about twice the mass found in full grown adult. Between 6 & 15 years of age the immune system of the blood becomes leading armor of body from disease. Tonsils are agglomerates of lymphoid tissue found at the beginning of pharynx. 3 pairs of tonsils, together they form a ring of lymphoid tissue at beginning of pharynx. Blood from absorptive areas of the gut tract is collected and delivered to the liver by the hepatic venous portal system. As blood passes through the sinusoids (channels) of the liver, it is acted upon by cells called Kupffer's cells, these cells line the sinusoids. Since Kupffer's cells remove harmful substance from the blood considered to be part of reticuloendothelial system.

The Kupffer cells were first observed by Karl Wilhelm von Kupffer in 1876. The scientist called them "Sternzellen" (star cells or hepatic stellate cell) but thought, inaccurately, that they were an integral part of the endothelium of the liver blood vessels and that they originated from it. In 1989, after several years of research, Tadeusz Browicz, a polish scientist, identified them, correctly, as macrophages. Their development begins in the bone marrow with the genesis of promonocytes and Monoblasts in to monocytes, and then on to peripheral blood monocytes, completing their differentiation in to Kupffer cells.

Red blood cells are broken down by phagocytic action, where the hemoglobin molecule is split. The globin's' chains are re-utilized, while the iron-containing portion, heme, is further broken down into iron, which is re-utilized and bilirubin, which is conjugated to glucuronic acid within hepatocytes and secreted in to the bile.

The receptor present in Kupffer's cells is the complement receptor of the immunoglobulin family (CRIg). Mice without CRIg could not clear complement system-coated pathogens. CRIg is conserved in mice and humans and is a critical component of the innate immune system.

Kupffer cell activation is accountable for early ethanol-induced liver injury, common in chronic alcoholics. Chronic alcoholism and liver injury deal with a two hit system. The second hit is characterized by an activation of the Toll-like receptor 4 (TLR4) and CD14, receptors on the transcription of pro-inflammatory cytokines (Tumor necrosis factor-alpha or TNF-α) and production of superoxide (a pro-oxidant). TNF-α will then cross the threshold the stellate cell in the liver, advantage to collagen synthesis and fibrosis will eventually cause cirrhosis, or loss of function of the liver. [6]

The complement system serves an important role in clearance of pathogens, immune complexes, and apoptotic cells present in the circulation. Complement fragments deposited on the particle surface serve as targets for complement receptors present on phagocytic cells. Although Kupffer cells, the liver resident macrophages, play a dominant role in clearing particles in circulation, complement receptors involved in this process have yet to be identified. Here we report the identification and characterization of a complement receptor of the immunoglobulin super family, CRIg that binds complement fragments C3b and iC3b. CRIg expression on Kupffer cells is required for efficient binding and phagocytosis of complement C3-opsonized particles. In turn, Kupffer's cells from CRIg-deficient mice are unable to efficiently clear C3-opsonized pathogens in the circulation, resulting in increased infection and mortality of the host. CRIg therefore represents a dominant component of the phagocytic system responsible for rapid clearance of C3-opsonized particles from the circulation. [7]

NANOPARTICLES

Nanoparticles are frequently studied as targeted drug carrier systems. The ability of these particles to circulate in the bloodstream for a prolonged period of time is often a prerequisite for fruitful targeted delivery. Toattainthis, hydrophilic stealth a polymers, such as poly (ethylene glycol) (PEG), are used as coating materials. Such polymers defense the particle surface and thereby diminish opsonization by blood proteins and uptake by macrophages of the mono nuclear phagocytic system. Yet, after localizing in the pathological site, nanoparticles should deliver their contents in an effectual manner to achieve a sufficient therapeutic response. The polymer coating, however, may hinder drug release and target cell interaction and can therefore be an obstacle in the realization of the therapeutic response. Attempts have been made to enhance the therapeutic efficacy of satirically balanced nanoparticle by means of shedding, i.e. a loss of the coating after arrival at the target site. Such an unmasking a process may enable drug release and/or target cell interaction processes. [8]

Formulation of transdermal delivery by using the nanoemulsion technology which a large quantity of drug can be incorporated in the formulation due to the high solubilization capacity. High permeation rate of the drug may be achieved by modifying the partitioning of drugs in favour of stratum corneum. [9]

The recently developed nanomelt technology involves size reduction of drug to nano size by milling the drug using a proprietary wet milling technique. The nano crystals of the drug are stabilized against agglomeration by surface absorption on selected

stabilizers, which are then incorporated into MDTs. Characteristics of this method is that it is used for poorly water soluble drugs. It leads to higher bioavailability and reduction in dose, cost effective manufacturing process. [10]

Drug delivery

A successful Drug delivery system of nanoparticle must be capable to target tumors which are localized outside MPS-rich organs. In the past decade, a great deal of work has been devoted to developing so-called "stealth" particles or PEGylated nanoparticles, which are invisible to macrophages or phagocytes. A foremost milestone in the pasture came when the use of hydrophilic polymers (such as polyethylene glycol, poloxamines, poloxamers, and polysaccharides) to efficiently coat predictable nanoparticle surface produced an opposing effect to the uptake by the MPS. These coatings provide a dynamic "cloud" of hydrophilic and neutral chains at the particle surface which repel plasma proteins. As a result, those coated nanoparticles become invisible to MPS, therefore, remained in the circulation for a longer period of time. Hydrophilic polymers can be introduced at the surface in two ways, either by adsorption of surfactants or by use of block or branched copolymers for production of nanoparticles.

PEG coated Nanoparticles

Nanoparticles containing a coat of PEG not only have a prolonged half-life in the blood compartment but also be able to selectively extravasate in pathological sites such as tumors or inflamed regions with a leaky vasculature. As a result, such long-circulating nanoparticles have heightened the potential to directly target tumors located outside MPS-rich regions. The size of the colloidal carriers as well as their surface characteristics are the hazardous to the biological fate of nanoparticles. A size less than 100 nm and a hydrophilic surface are life blood in entireness the downgrading of opsonization reactions and subsequent clearance by macrophages. Coating conventional nanoparticles with surfactants or PEG to obtain a long-circulating carrier has now been used as a standard strategy for drug targeting *in vivo*.

In "active targeting" of nanoparticles in order to deliver drugs to the right targets, based on molecular acceptance processes such as ligand-receptor or antigen- antibody interaction. Considering that fact that folate receptors are over expressed on the surface of some human malignant cells and the cell adhesion molecules such as selections and integrin's are involved in metastatic events, nanoparticle bearing specific ligands such as folate may be used to target ovarian carcinoma while specific peptides or carbohydrates may be used to target integrin's and selections.

Targeting with small ligands appears more likely to succeed they are easier to handle and manufacture. Furthermore, it could be advantageous when the active targeting ligands are used in combination with the long-circulating nanoparticles to maximize the likelihood of the success in active targeting" of nanoparticles. [11]

Monocular Phagocytic System (MPS)

This is a common problem is nanoparticle as they are rapidly taken up by the macrophages of the so- called monocular phagocytic system (MPS) (also known as the Reticuloendothelial system (RES) and accumulate mainly in the liver, spleen, and lungs, whereas other targets in the body are much harder to reach. Great efforts have been tackled to overcome this rapid uptake by the liver and other parts of the MPS. The most successful strategies to prevent the rapid RES uptake are coating of the particles with surfactants or covalent linkage of polyoxyethylene chains to their surfaces. The properties of some of these systems to achieve prolonged blood circulation times are often referred to as "stealth" properties acknowledging their non-recognition by the MPS. However, keeping these colloidal drug carriers in the blood circulation for extended times does not necessarily mean that they reach their desired therapeutic target site. In order to reach this objective other strategies may have to be employed. [12]

In intravenously injected colloidal carriers, such as liposomes and polymeric nanospheres from the blood by Kupffer's cells, has initiated a flow of development for Kupffer's cell- evading" or long -circulating particles. Such carriers have applications in vascular drug delivery and release, site- specific targeting (passive as well as active targeting), as well as transfusion medicine. Reviewed and assessed for engineering and design of long-circulating carriers, we have taken a lead from nature. Here, we have explored the surfaces mechanisms, which afford red blood cells long circulatory lives and the ability of specific microorganisms to evade macrophage recognition. In fabricated of a wide range of particulate carriers (such as Nano spheres, nanoparticle, micelles, oil-in-water emulsions) this has prolonged circulation and/or target specificity. With regard to the targeting issues, attention is particularly focused on the importance of physiological barriers and disease states. [13]

Nano drug delivery systems (NDDS) can transport anticancer agents to tumor sites via enhanced permeability and retention (EPR) effect to enhance the therapeutic effect and reduce side effects. To give full play of the EPR effect, long- term circulation of NDDS is needed, since it provides the NDDS with better chance to reach and interact with tumor. The blood circulation time of NDDS is determined by their combination properties, such as size, shape, stiffness, surface shielding etc., all of which are important and needed to be considered in designing long-circulating NDDS. [14]

Prolonged circulation time of Nanoparticle

To allow well organized of specific processes, numerous factors should be taken in to account the majority of them connected to pharmacokinetics and/or bio distribution. Upon their intravenous

administration, nanoparticles can be delivered over organs and tissues, hunted by rapid renal clearance when the hydrodynamic diameter is less than 5.5 nm, as shown in rodent models. Most nanoparticle agents have a hydrodynamic diameter that is considerably superior, causing them to be cleared from the blood stream predominantly by the Monocular phagocytic system of the liver and spleen. The early elimination of the nanoparticles occur through their binding to opsonin proteins in the circulation and their subsequent uptake by the Monocular phagocytic system, which can be useful for targeting the liver but represents a substantial obstacle for efficient targeting of atherosclerotic plaques. To ensure efficient targeting of plaques, rapid removal of nanoparticles by the Monocular phagocytic system should be prevented to prolong their circulation time in the blood, enabling nanoparticles to reach and accumulate in tissues and exert their effects. Specific size, surface charge and stability can all contribute to enhanced circulatory half-life. One of the most commonly used methods to evade rapid clearance via the Monocular phagocytic system is the addition of hydrophilic polymers such as polyethylene glycol (PEG) to the surface of the nanoparticle. In addition to PEG, various alternative polymers some of which are biodegradable are under investigation for the same purpose. [15]

Surface modified nanoparticle

Lipid- conjugates of two amphipathic polymers, poly (2-methyl-2-oxazoline) (PMOZ) and poly (2-ethyl-2-oxazoline) (PEOZ) (degree of polymerization approximately 50) were synthesized by linking glutarate esters of the polymers to distearoylphosphatidylethanolamine (DSPE) or alternatively by termination of the polymerization process with DSPE. Surface modified Nanoparticle (90±5 nm) prepared from either conjugate (5 mol % of total lipid) were injected in to rats and followed by blood level and tissue distribution measurements. Both polymers PEOZ and PMOZ were found to convey long-circulation and low hepatosplenic uptake to nanoparticle to the same extent as polyethylene glycol (PEG), the best known material for this purpose. This is the first demonstration of protection from rapid recognition and clearance conveyed by alternative polymers, which is equal to the effect of PEG. [16]

Over the last few decennia, nanocarriers for drug delivery have materialized as powerful tools with absolute hypothetical to improve the therapeutic efficacy of anticancer drugs. Many colloidal drug delivery systems are under development to ameliorate the site specificity of drug action and reduce the systematic side effects. By virtue of their small size they can be injected intravenously and disposed in to the target tissues where they release the drug. Nanocarriers interact immensely with the adjacent environment, namely, endothelium vessels as well as cells and blood proteins. Consequently, they are rapidly removed from the circulation mostly by the Monocular phagocytic system. In order to endow nano systems with long circulation properties, new technologies aimed at the surface modification of their physicochemical features have been developed. In particular, stealth nanocarriers can be obtained by polymeric coating. In this paper, the basic concept underlining the "stealth' 'properties of drug nanocarriers, the parameters influencing with the colloid surface, the most usually used materials for the coating process and the outcomes of this abnormal procedure are thoroughly discussed. [17]

Surface charges on colloidal particles

The surface charges on biodegradable albumin nanoparticles were introduced by covalent coupling different primary amines to examine their influence on phagocytosis by macrophages under *in-vitro* conditions. Albumin particles with a zeta potential close to zero showed a reduced phagocytic uptake in comparison with charged particles, especially nanoparticles with a positive zeta potential. The phagocytic uptake in the present study was examined using an established cell culture model based on primary mouse peritoneal macrophages and a human hematopoietic monocytic cell line (U-937) treated with phorbol-12-myristic-13-acetate to induce cell differentiation. The influence of opsonins on *in-vitro* phagocytes experiments was characterized using carriers pre- treated with human serum. In the presence of human serum the phagocytic activity of U-937 cells was found to be similar to primary mouse macrophages without serum. In contrast to peritoneal macrophages, U-937 cells showed no phagocytic activity in the absences of serum. In particular, only the C3b-complement deposition on the particle surface seems to promote the phagocytic process. The *in-vitro* distribution of albumin carriers in rats was investigated using magnetic resonance imaging (MRI). No differences in blood circulation times and organ accumulation between different nanoparticle preparations with positive, neutral and negative surface charges could be observed in rats, suggesting that the *in vivo* fate of albumin nanoparticles is significantly influenced by factors not reflected in the *in-vitro* cell culture models. [18]

Theranostics

Nanoparticles represent highly auspicious platforms for the development of imaging and therapeutic agents, including those that can either be detected *via* more than one imaging technique (multi-modal imaging agents) or used for both diagnosis and therapy (Theranostics). A fore most obstacle to their medical application and translation to the clinic, however, is the fact that many acquire in the liver and spleen as a result of opsonization and scavenging by the Monocular phagocytic system. This focused review summarizes recent efforts to develop zwitterionic-coatings to counter this issue and render nanoparticles more biocompatible. Such coatings have been found to greatly reduce the rate and/or extent of non-specific

adsorption of proteins and lipids to the nanoparticle surface, thereby inhibiting production of the "biomolecular corona" that is proposed to be a widespread feature of nanoparticles within a biological environment. Additionally, *in-vivo* studies have demonstrated that larger-sized nanoparticle with a zwitterionic coating have extended circulatory lifetimes, while those with hydrodynamic diameters of ≤5nm exhibit small-molecule-like pharmacokinetics, residual sufficiently small to pass through the fenestrae and slit pores during glomerular filtration within the kidneys, and enabling efficient excretion *via* the urine. The larger particles speak for ideal candidates for use as blood pool imaging agents, whilst the small ones provide a highly promising platform for the future development of Theranostics with reduced side effects profiles and superior dose delivery and image contrast capabilities. [19]

First, we describe the colloidal and hydrophilic coating materials investigated, with particular focus on the literature concerning particles other than nanoparticle. Then the pharmacokinetics and bio distribution of these MPS-opposing systems are summarized. Finally, the mechanism behind the MPS-avoidance phenomenon is discussed in the light of the concept of steric stabilization. [20]

Biodegradable Nanoparticles

The methods of preparation of biodegradable nanoparticles, different factors affecting optimal drug encapsulation, factors affecting drug release rates, various surface modifications of nanoparticles to enhance *in-vivo* circulation, distribution and multimodal functionalities along with the specific applications such as tumor targeting, oral delivery, and delivery of these particles to the central nervous system have been carrier for site specific delivery of vaccines, genes, drugs and other biomolecules in the body. They offer enhanced Biocompatibility, superior drug/ vaccine encapsulation, and convenient release profiles for a number of drugs, vaccines and biomolecules to be used in a variety of applications in the field of medicine.

Macrophages

One of the problems faced in the use of nanoparticles *via* the intravenous route was their speedy removal by the phagocytic cells (Macrophages) in the body. Macrophages are powerful phagocytic cells and the important constituent of Monocular phagocytic system (MPS). The Monocular phagocytic system (MPS) is one of the body's innate defenses. MPS filters and eliminates any injected particulate matter including nanoparticles from the blood stream if they are recognized as foreign body. Unless the injected nanoparticles are modified in a way to escape recognition as foreign particles, they will be phagocytized and removed from the circulation. This necessitated modification of the surface of nanoparticles in order for them to escape MPS recognition and subsequent clearance. Surface modification of the nanoparticles therefore plays a critical role in their successful applications *in-vivo*. Once nanoparticles are Surface modified with biomolecules found normally in the body; they will be able to circulate within the blood vascular system for longer period of time. This increases the probability of nanoparticles reaching their target rapidly and safely when compared to non-modified nanoparticles. Smaller particles (<100 nm) circulating in blood vascular system with a hydrophilic surface have the greatest ability to evade the MPS. Several methods have been developed for Surface modification of the nanoparticles. The most preferred method of Surface modification is the adsorption or grafting of poly-ethylene glycol (PEG) to the surface of nanoparticles. Addition of PEG and PEG containing copolymers to the surface of nanoparticles results in an increase in the blood circulation half-life of the particles. The exact mechanisms by which PEG prolonged circulation time of the Surface modified nanoparticles are still not well understood. It is generally thought that the increased residency of the nanoparticles in blood is mainly due to prevention of opsonization of nanoparticle by a certain serum or plasma proteins (opsonins). It is believed that PEG causes steric repulsion by creating hydrated barriers on nanoparticle surfaces that prevents coating of PEG modified nanoparticles by serum opsonins.

POLYMER

Studies have shown that the degree to which proteins (opsonins) adsorb on to particle surface can be minimized by increasing the PEG density on the particle surface. Increasing the molecular weight of the PEG chains has also been she own to minimize opsonization of nanoparticle and improve retention in the circulation. For example, Leroux *et al*. showed that an increase in PEG molecular weight was associated with less interaction with the MPS, and longer systemic circulation of PLGA nanoparticles. PEG has been shown to impart stability on PLA particles submerged in simulated gastric fluid (SGF). Tobio *et al*. showed that after 4 hours in SGF, 9% of PLA particles converted to lactic acid versus 3% conversion for PEG- particles. PEG is also believed to facilitate mucoadhesion and consequent transport through the peyer's patches of the GALT (gut associated lymphoid tissue). In addition, PEG may benefit nanoparticle interaction with blood constituents. Thus, the presence of PEG on the nanoparticles imparts additional functionality during the use of polymeric nanoparticles.

Hydrophilic Polymers

A Parts from PEG, there are other Hydrophilic Polymers such as poloxamers, polysorbate 80, TPGS, polysorbate 20, polysaccharides like dextran and different type of copolymers that can be used to efficiently coat conventional nanoparticles to add number of variations in the surface properties of nanoparticles. These coatings provide a dynamic cloud of hydrophilic and neutral chains at the particle surface, which repels plasma proteins. Surface modification by

TPGS Increases the adhesion of nanoparticles to tumor cell's surfaces, it also provides safer environments to the encapsulated proteins. IgG coating on the surface of nanoparticle Increases the immune response to the encapsulated proteins within the nanoparticles. Hydrophilic Polymers can be applied at the surface of NPS by adsorption of surfactants or by use of block copolymers or branched copolymers. [21]

Nanoparticles Impact on Pharmacokinetics and Pharmacodynamics

Nanoparticles (NPs) provide several advantages over the small molecule drugs including prolonged circulation time and enhanced delivery to targeted sites. Once ANP enters the body, it interacts with host's immune system and is engulfed by cells of the Monocular phagocytic system (MPS). The interaction between NPs and the immune cells can result in immune suppression, which may enhance or reduce the treatment effects of NPs. Therefore, it is critical to understand the interactions between NPs and the immune system in order to optimize the treatment benefit and minimize the undesirable toxicities of NPs. This review elaborates on the interaction between NP and the MPS and its impacts on the Pharmacokinetics (PK) and Pharmacodynamics (PD) of NPs and applications for inflammatory diseases. This review also encompasses an overview of NPs being developed for treatment of inflammatory diseases. [22]

While plasma proteins can influence the physicochemical properties of nanoparticles, the adsorption of protein to the surface of nanomaterial's can also alter the structure and function of the protein. Here, we show that plasma proteins form a hard corona around synthetic layered silicate nanoparticles (LSN) and that one of the principle proteins is serum albumin. The protein corona was required for recognition of the nanoparticles by Scavenger receptor family associated with the Monocular phagocytic system (MPS). Albumin alone could direct nanoparticle uptake by human macrophages, which involved class a but not class B Scavenger receptors. Upon binding to LSN, albumin unfolded to reveal a cryptic epitope that could also be exposed by heat denaturation. This work provides an understanding of how albumin, and possibly other proteins, can promote nanomaterial's recognition by the MPS without albumin requiring chemical modification for scavenger receptor recognition. These findings also demonstrate an additional function for albumin *in-vivo.* [23]

Nanoparticles (NP) uptake by the Monocular phagocytic system (MPS) has been described through several *in-vitro* and *in-vivo* studies, and is a field of research that is constantly evolving and continuing to grow. While many NP agents contain traditional small molecules that have been used therapeutically for decades, the unique delivery system of NPs allows for greater exposure and efficacy of the active chemical entity in the body. Once an NP enters the body, they encounter a much different host response than that observed with small molecule administration. The network of opsonins and circulating and tissue phagocytes is very complex, and their interaction with NPs often depends on the biological atmosphere as well as the physicochemical properties of the NP. This chapter will discuss NP uptake by the MPS and the resulting clinical manifestations. More specifically, key concepts will include differences in NP physicochemical properties, cell lines and/or animal models used, and the bidirectional interaction between the MPS and NPs in patients. [24]

The literature reviewed provides enough promise for anticipating therapeutic and diagnostic applications of surface -modified nanoparticles. In an overview of recent advances in the surface modification of colloidal particles to oppose uptake by the Monocular phagocytic system (MPS) is presented. Nanoparticles (NPs) provide several advantages over the small molecule drugs including prolonged circulation time and enhanced delivery to targeted sites. Once a NP enters the body, it interacts with host's immune system and is engulfed by cells of the Monocular phagocytic system (MPS). The interaction between NPs and the immune cells can result in immune suppression or immune stimulation, which may enhance or reduce the treatment effects of NPs. Therefore, it is critical to understand the interactions between NPs and the immune system in order to optimize the treatment benefit and minimize the undesirable toxicities of NPs. We conclude that the literature review provides enough promise for anticipating therapeutic applications of surface-modified nanoparticles.

REFERENCES

1. Devalapally H, Chakilam A, Amiji MM. Role of Nanotechnology in Pharmaceutical Product Development. Journal of Pharmaceutical Science 2007; 96(10): 2547-65.
2. http:/ / www. Britannica.com/bps/user- profile/4419/the-editors-of-encyclopedia-Britannica.
3. Knight J, Nigam Y. The Lymphatic System Part 3 – The Lymphatic System and Immunity. NT 2008; 104(15): 22-23.
4. Deodhar MS, Shirode AR, Kadam VJ. High Performance Nanoparticles Fluid Suspensions (Nanofluide): A Future of Pharmaceutical Nanotechnology. International Journal of Pharmaceutical Science and Drug Research 2014; 6(4): 263-270.
5. Chandrababu D, Patel HB, Patel HL, Dimeshbhai MJ. A review on pharmaceutical nanotechnology. Asian Journal of Pharmacy and Life Science 2012; 2(2): 324- 338.
6. Kupffer cell. From Wikipedia, the Free Encyclopedia.
7. Helmy KY, Katschke KJ Jr, Gorgani NN, Kljavin NM, Elliott JM, Diehl L, Scales SJ, Ghilardi N, van Lookeren Campagne M. CRIg: A Macrophage Complement Receptor Required for Phagocytosis of Circulating Pathogens. Cell 2006; 124: 915-927.
8. Romberg B, Hennink WE, Storm G. Sheddable Coatings for Long Circulating Nanoparticles. Pharm Res. 2008; 25(1): 55-71.
9. Talegaonkar S, Tariq M, Alabood RM. Design and Development of O/W Nanoemulsion for the Transdermal Delivery of Ondansetron. Bulletin of Pharmaceutical Research 2011; 1(3):18-30.
10. Yadav AK, Sharma A, Saxena S, Kesarwani A. Mouth Dissolving Tablets: General Overview and Formulation

Aspects. Bulletin of Pharmaceutical Research 2014; 4(1): 43-57.
11. Mohanraj VJ, Chen Y. Nanoparticles - A Review. Tropical Journal of Pharmaceutical Research 2006; 5(1): 561-573.
12. Kreuter J. Coating of Nanoparticles with Surfactants: Targeting Versus Prolonged Circulation. Targeting of Drugs 6, NATO ASI Series. 1998; 300: 253-261.
13. Moghimi SM, Hunter AC, Murray JC. Long-Circulating and Target-Specific Nanoparticles: Theory to Practice. Pharmacological Reviews 2001; 53(2): 283-318.
14. Wei W, Jiang X. Wei W, Jiang X. Functional nanoparticles for bioanalysis, nanomedicine, and bioelectronic devices. Volume 2, ACS Symposium Series, Vol. 1113, Chapter 2, pp. 27–36. 4, 5.
15. Lobatto ME, Fuster V, Fayad ZA, Mulder WJM. Perspectives and Opportunities for Nano Medicine in the Management of Atherosclerosis. Nature Reviews Drug Discovery 2011; 10(11): 835-852.
16. Woodle MC, Engbers CM, Zalipsky S. New Amphipatic Polymer-Lipid Conjugates Forming Long-Circulating Reticuloendothelial System-Evading Liposomes. Bioconjug Chem 1994; 5(6): 493-496.
17. Salmaso S, Caliceti P. Stealth Properties to Improve Therapeutic Efficacy of Drug Nanocarriers. Journal of Drug Delivery 2013; Article ID 374252: 19 pages.
18. Roser M, Fischer D, Kissel T. Surface-Modified Biodegradable Albumin Nano-and Microspheres. II: effect of surface charges on *in vitro* phagocytosis and Biodistribution in rats. European Journal of Pharmaceutics and Biopharmaceutics 1998: 46(3); 255-263.
19. Garcia KP, Zarschler K, Barbaro L, Barreto JA, O'Malley W, Spiccia L, Stepphan H, Graham B. Zwitterionic Coated "Stealth" Nano Particles for Biomedical Applications: Recent Advance in Countering Biomolecular Corona Formation and Uptake by the Mononuclear Phagocyte System. Small 2014; 10(13): 2516-2529.
20. Storm G, Belliot SO, Daemen T, Lasic DD. Surface Modification of Nanoparticles to Oppose Uptake by the Mononuclear Phagocyte System. Advanced Drug Delivery 1995; 17(1): 31-48.
21. Mahapatro A, Singh DK. Biodegradable Nanoparticles are Excellent Vehicle for Site Directed *In-vivo* Delivery of Drugs and Vaccines. Journal of Nano biotechnology 2011; 9: 55.
22. Song G, Petschauer JS, Madden AJ, Zamboni WC. Nanoparticles and the Mononuclear Phagocyte System: Pharmacokinetics and Applications for Inflammatory Diseases. Current Rheumatology Reviews 2014; 10(1): 22-34.
23. Mortimer GM, Butcher NJ, Musumeci AW, Deng ZJ, Martin DJ, Minchin RF. Cryptic Epitopes of Albumin Determine Mononuclear Phagocyte System Clearance of Nanomaterials. ACS Nano 2014; 8(4): 3357–3366.
24. Caron WP, Rawal S, Song G, Kumar P, Lay JC, Zamboni WC. Bidirectional Interaction between Nanoparticles and Cells of the Mononuclear Phagocytic System. Handbook of Immunological Properties of Engineered Nanomaterials 2013; 1: 385-416.

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