International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 2127-2144 www.ijprajournal.com ISSN: 2249-7781

Formulation Strategies against Opsonization Recognition: Prerequisite for Long Circulatory Systemic Drug Delivery

[1]Mohini Rawat, [2]Nandan Singh Bisht, [1]Saloni Jaswal, [1]Rupali Joshi, [1]Ajay Singh Bisht

1. Department of Pharmaceutics, Himalayan Institute of Pharmacy and Research, Rajawala, 248007, Dehradun, India.

2. Nanomedicine research centre, Department of Pharmaceutics, I.S.F. College of Pharmacy, Moga, 142001, Punjab, INDIA.

Submitted: 15-02-2023 Accepted: 25-02-2023

ABSTRACT

An appropriate therapeutic strategy against systemic infections associated with chronic immunodeficiency disease possesses a great challenge for medical professionals. Long circulatory carrier systems offer a viable alternative to address the challenges related to systemic infections. However, the clinical success of aforesaid strategy depends on how efficiently the carrier system disguised the opsonisation process. There are several variables such as molecular weight, lipophilicity, antigenicity, size, shape, bio-chemical nature, etc. reported to be play an important role in the opsonisation process. Taking above factors into consideration lot of efforts have been made by the formulation scientist to design a suitable carrier system to achieve the desired therapeutic goal. This review provides an interface of the opsonisation process and the formulation strategy for making a suitable carrier system against systemic infections.

I. INTRODUCTION

Over the past few decades, we have observed a surge in development of long circulating vehicles within the nanoscale size range. By keeping the carrier system in the blood stream for long enough improves the therapeutic outcomes and decrease the unwanted side effects of drugs, particularly useful in delivery of potent and anticancer drugs. However, opsonization, a body's natural defence mechanism against invader mediated through RES (reticulo-endothelial cells) is a major obstacle for making the carrier system long circulatory.The immune reaction cascade is initiated with the adsorption of opsonin's to the surface of nanoparticles and in doing so, aid their clearance via phagocytosis. Opsonin's are specific proteins related to immune system such as immunoglobulin's or complement proteins. Without the presence of adsorbed opsonin proteins, the phagocytes naturally will not be able to bind or identify the foreign particles(Owens III and Peppas, 2006). As per general rule, the opsonin proteins can recognise hydrophobic particles more rapidly as compared to hydrophilic particles due to enhanced absorbability of blood serum proteins on hydrophobic surfaces (Carrstensen et al., 1992, Norman et al., 1992). Other than opsonisation the intravenously administered nanoparticles can be eliminated from the systemic circulation via adsorption mediated endocytosis. Adsorption mediated endocytosis triggered by interaction between the positively charged nanocarrier and the negatively charged cell membrane (Sahay et al., 2010).

The approaches utilized for making long circulatory nanoparticles involve the coating of PEG (poly ethylene glycol) (Yadav et al., 2011), dextran sulphate (Kotagiri et al., 2013), combined coating of PEG and water-soluble chitosan (Sheng et al., 2009), coating of biomimetic entities i.e. body's own long circulating entities such as RBC membrane coated nanoparticles (Fang et al., 2012), heparin or dextran surface bearing poly(methyl methacrylate)nanoparticles (Passirani et al., 1998), biomimetic mucin modified PLGA nanoparticles (Thasneem et al., 2013). The current gold standard for imparting long-circulating features involves the use of PEG, which surrounds the particles with a hydrophilic layer and thus prevents recognition by the mononuclear phagocyte system. Recently, a new strategy for synthesizing biomimetic nanoparticles has been inspired by the body's own long-circulating entities, red blood cells (RBCs) (Fang et al., 2012). Many of thesesystems utilises surface modification with biomolecules or hydrophilic polymers to escape from opsonisation.However, product stability, scale-up and feasibility of applications are the major

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 2127-2144 www.ijprajournal.com ISSN: 2249-7781

concern to make these strategies realistic and applicable.

To obtain successful long circulatory nanoparticles, most importantly we need to understand the factors that influence blood circulation time and biodistribution of nanoparticles. Herein particle size, shape, surface charge, hydrophilicity and surface modification of nanoparticles have been considered as key factors affecting the retention time in blood circulation and organ distribution of nanoparticles. These factors if maintained up to an optimized level can contribute to make the nanoparticles long circulatory by delaying opsonization thus escaping from reticuloendothelial system.

II. OPSONIZATION PROCESS

The process of opsonization is one of the major obstacles for intravenously administered polymeric nanoparticles. The opsonisation process begins when nanoparticles are administered via intravenous injection (I.V.), with the adsorption of opsonin proteins present in the blood serum to the surface of nanoparticles and by doing so, allowing macrophages of the mononuclear phagocytic system (MPS) to easily recognize and remove these polymeric nanoparticles before they can perform their designed therapeutic function. Together these two processes form the main clearance mechanism for the elimination of undesirable components larger than the renal threshold limit from the blood. If the polymeric nanoparticles are non-biodegradable, that cannot be destroyed by the process phagocytosis then sequestration of MPS organs typically occurs which leads to the toxicity and other negative side effects(Ilium et al., 1986, Peracchia et al., 1999, Plard and Bazile, 1999).

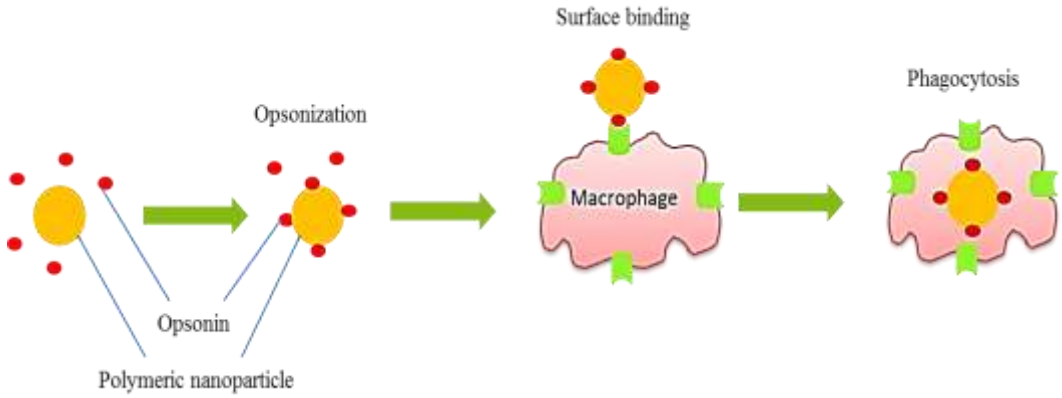

Figure-1 Process of opsonisation and phagocytosis.

The longevity in the circulation of polymeric nano-carriers is strongly affected by physical interactions with specific components present in blood circulation that are opsonins. These components include complement proteins such as C3, C4, and C5 are known to be common opsonins along with other blood serum proteins such as laminin, fibronectin, C-reactive protein, type I collagen, and immunoglobulin(Frank and Fries, 1991, Johnson, 2004, Ratner et al., 2004). The opsonin's play a major role in the clearance of foreign particles as indirectly confirmed in many in-vivo animal studies of inherited and induced C3 deficient animal models. For example, research has revealed that these animal models are often times more susceptible to certain diseases which are easily controlled by phagocytosis in non-C3 deficient animal models (Singer et al., 1994).

The mechanism of binding of opsonins on the surface of polymeric nanoparticles or Nano vehicles include any of several attractive forces such as van der wall, electrostatic, ionic, hydrophobic/hydrophilic and other forces. After binding of opsonins the next step is the attachment of opsonized particles to the macrophage via surface bound opsonins. Without surface bound opsonin proteins the macrophages will typically not be able to recognize the foreign particles. The method of macrophage attachment may be specific, non-specific or complement activation. Phagocytic cells contain specialized receptors that can interact with specific opsonin proteins. The second method of attachment involves the non-specific binding of phagocytes to surface adsorbed blood serum proteins which can result in the stimulation of phagocytosis as well(Frank and Fries, 1991) The third significant method of phagocytic attachment

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 2127-2144 www.ijprajournal.com ISSN: 2249-7781

is complement activation. The complement system can be activated by one of several mechanism including the classical, alternative and lectin pathway.

The classical complement pathway requires the presence of antibodies, either as immunoglobulin (IgG or IgM) bound to cell surface antigen (Ag) or as an Ag-Ab immune complex. The serum protein C1 binds to the antibody, which in turn results in activation of C4, C2, and C3, and leads to the formation of C5, C6, C7, C8 and C9. This eventually leads to the formation of the C5-C9 membrane attack complex (MAC), which lyses and destroys the cell. The alternative pathway can be initiated with the complete absence of antibodies and is naturally activated by the binding of C3 fragments to the surface of the pathogen. The lectin pathway is activated by the binding of mannose-binding lectin on mannose contained on the surface corona of bacteria and viruses. Although a few hypotheses have been proposed to elucidate the presence of supplementary activation pathways, they have not been fully explained.

Regardless of the activation pathway, the enzymatic cascade of the complement activation leads to the formation of a common enzyme, C3 convertase, which cleaves the central protein of the complement system, the third component C3(Sahu and Lambris, 2001). The fragment C3b of C3 is the crucial active component that triggers the cleavage of a variety of complement proteins (C5–C9). The assembly of these proteins contributes to the formation of the membrane attack complex (MAC) that is able to destabilize bacteria, viruses, and nanocarriers for drug delivery.

The third and final step in the clearance process is the ingestion of foreign materials by phagocytes. This step in the process typically involves the endocytosis of the particle or foreign material by a phagocyte. Following endocytosis of the particle, the phagocytes will begin to secret enzymes and other oxidative-reactive chemical factors, such as superoxides, oxyhalide molecules, nitric oxide, and hydrogen peroxide, to break down the phagocytosed material (Mitchell, 2004).

Although, the process of opsonisation is directed to the natural body protection from the unwanted foreign particles that includes virus, bacteria and other disease causing microorganisms or particulates but in addition this process promotes the removal of circulating drug carriers as well that remains a major obstacle to achieve appropriate systemic therapeutic drug concentration.

III. PHYSICOCHEMICAL PROPERTIES AFFECTING OPSONISATION PROCESS

3.1 Size

The in vivo fate of nanoparticles depends on their size. Particle size is known to be inherently related to the rate of clearance from the blood circulation as smaller particles ranging 70-200 nm (Stolnik et al., 1995, Alexis et al., 2008) shows higher retention in blood stream. Nanoparticles ranging less than 5 nm in diameter are typically eliminated from the blood circulation by renal clearance (Vinogradov et al., 2002, Choi et al., 2007) which leads to short blood half-lives. Mostly the optimized size of nanocarriers used in nanomedicine normally ranges from 20 to 200 nm, as NCs greater than 200 nm would be more efficiently captured by the RES and may cause embolization in the liver and lung while those lesser than 100 nm would escape from the blood vessels through fenestrations in the endothelial lining (Stolnik et al., 1995). As the matter of fact, due to the heterogeneity in size it is hard to identify a specific threshold for NCs to adapt the long circulatory effect.Another conceivable explanation is that size reliant on biodistribution might have more to do with a simple filtering effect, whereby larger particles are eliminated by the spleen and liver more quickly while smaller particles are concentrated to the bone marrow (Moghimi et al., 1993a).

3.2 Shape

The shape intravenously administered nanocarriers remains mostly ignored characteristic that is also taken to be an important factor affecting blood circulation time(Fox et al., 2009, Sharma et al., 2010, Merkel et al., 2011). Disk like, cylindrical, and biconcave particles might be more effectual than spherical ones at minimizing cellular as well as phagocytic uptake. Research revealed that the initiation of macrophage internalization is depend on the local shape of the particle at the position of attachment rather than the overall shape (Champion and Mitragotri, 2006).For example, an elliptical particle internalized within few minutes if the attachment to macrophage at the pointed end while flat region attached particles remain intact for longer period of time. Shape, contact area, volume, local curvature of the particle at the contact point and the orientation of the particle are critical to the nature of interaction with blood components as well as blood vessel wall.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 2127-2144 www.ijprajournal.com ISSN: 2249-7781

In recent study pegylated gold nanoparticles (spherical shaped) and rod shaped particles were compared and it was found that the gold nanorods have minimum uptake by liver and had longer circulation time than gold nanoparticles in blood stream(Janát-Amsbury et al., 2011, Merkel et al., 2011). Doshi et a in 2009 prepared biconcave shaped microparticles, and postulated that the mechanobiological mimicry of RBCs can increase the elasticity and blood circulation time of intravenously administered nanocarriers(Doshi et al., 2009). Recently, the tumor distribution kinetics of nanorods with a sizeof 44nm were compared to those of 35nm nanospheres showing the similar hydrodynamic radius (Chauhan et al., 2011). In spite of similar blood circulation profiles, the nanorods were shown to extravasate to the interstitium 4 times faster and to diffuse deeper in the tumor as compared to nanospheres.

3.3 Surface charge

Surface charge is one of the surface characteristic that can affect the in-vivo fate of nanocarriers after intravenous administration. The overall plasma circulation profile along with opsonisation profile and recognition of the intravenously administered particles by organs of the MPS can be altered by the existence of charge present on the surface of particles (Alexis et al., 2008, Salvador-Morales et al., 2009, Bertrand and Leroux, 2012) The nanocarriers surface may be of anionic, cationic or of neutral charge that is depend upon polymer used for the fabrication of nanocarriers. Roser et al in 1998 demonstrated in his research that the charged particles are easily recognized by opsonin proteins and subsequently phagocytized by mononuclear phagocytic system (MPS) then neutrally charged particles (Roser et al., 1998). The clearance of nanocarriers by MPS bearing negative surface charge canincreased, decreased or have no influence (Yamamoto et al., 2001, Levchenko et al., 2002, Arvizo et al., 2011), but particles with positive charges are mostly recognized by plasma proteins and rapidly cleared off from the systemic circulation (Campbell et al., 2002, He et al., 2010, Xiao et al., 2011). Moreover positive charged particles interact with negatively charged luminal surface of blood vessel wall that results in rapid clearance from the blood circulation (Maeda, 1994, He et al., 2010).Furthermore cationic nanocarriers are more likely to produce toxic effects than anionic nanocarriers (Wei et al., 2012). For example, in the presence of definite concentrations of unshielded primary amines (positive charge), haemolysis was observed on the surface of carbosilane, poly-amidoamine, poly-lysine and polypropylene imine (Malik et al., 2000, Shah et al., 2000, Domański et al., 2004, Agashe et al., 2006, Bermejo et al., 2007, Dutta et al., 2007).

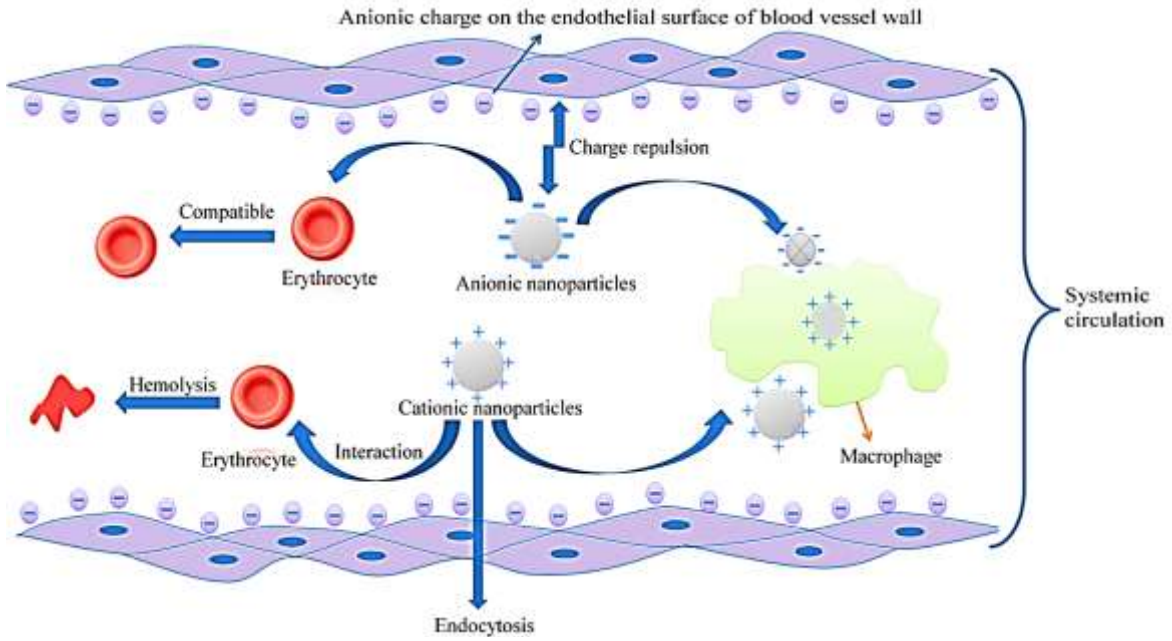

Figure-2 Fate of charged nanoparticle in systemic circulation.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 2127-2144 www.ijprajournal.com ISSN: 2249-7781

IV. PREREQUISITE FEATURES FOR LONG CIRCULATORY CARRIER SYSTEM

It is well known that the biocompatibility of intravenously administered particles depends on the physical and chemical properties i.e. size, shape and surface chemistry as well as the physiological environment it came into contact(Dobrovolskaia and McNeil, 2007, Dobrovolskaia et al., 2008, Aggarwal et al., 2009).Kohane and Langer in 2010 defines biocompatibility of any material as "an expression of the benignity of the relation between a material and its biological environment" (Kohane and Langer, 2010).However some researchers modify this definition in context of delivery system as the acceptable functionality of biomaterial in a physiological environment is important. In short high degree of biocompatibility is attained when a material interact with body without inducing any adverse effect i.e. toxic immunogenic, carcinogenic and thrombogenic. Thus during the initial characterization of the intravenously administered particles it is most important to evaluate the nanoparticles hematocompatibility. ISO-10993 internationally recognized standard indorses using the following in-vitro tests to observe hematocompatibility of intravenously administered nanomedicines: tests for hemolysis, thrombogenicity (this includes effects on platelets) and complement activation.

4.1 Hemolysis

The mechanisms for drug mediated haemolysis include nonimmunogenic (e.g., via direct drug–erythrocyte membrane interactions) and immune mediated (e.g., by a drug-specific antibody) hemolysis. Red blood cells (erythrocytes) occupied in a larger volume fraction in blood stream than other blood components so the probability of interaction with intravenously administered particle is higher. Such interaction ultimately leads to adverse physiological outcome (severe hemolysis may cause life threatening conditions such as anemia), require the need for the examination of haemolytic activity that remains an imperative aspect of preclinical characterization of nanoparticles. Many authors stated hemolytic effects of different nanoparticles in the literature, as many of the studies have been conducted with blood to see the early toxic effects of nanoparticles especially cationic charged particles(Malik et al., 2000, Shah et al., 2000, Domański et al., 2004, Agashe et al., 2006, Bermejo et al., 2007, Dutta et al., 2007).For example, among a set of similar-sized fullerenes (C60- derivatives) bearing different numbers of anionic and cationic surface moieties, it was found that the haemolytic tendency proportionally increasing with increasing the cationic surface groups (positive surface charge) and the anionic charged groups were found safe(Agashe et al., 2006).

4.2 Thombogenicity

Certain intravenously administered nanocarriers often require surface engineering to extend the systemic circulation time in order to achieve the desired therapeutic outcome. Longer the circulation time longer will be the contact with components of the coagulation system (i.e.mixture of red blood cells, aggregated platelets, fibrin and other cellular elements). The interaction between the administered nanocarriers with these components results in activation of coagulation cascade which ultimately leads to partial or complete blocking of a blood vessel by thrombus(Movat et al., 1965).In-vitro analyses of platelet aggregation and plasma coagulation time include the incubation of nanoparticles with platelet-rich plasma which is obtained from freshly derived human whole blood. Then the plasma is inspected using a particle count and size analyser to define the number of active platelets. Finally the percent aggregation of platelet will be calculated by comparing the active platelats associated with the nanoparticles sample to control plasma (Neun and Dobrovolskaia, 2011).The effect of nanocarriers surface characteristics on thrombogenic property is not currently available comprehensively; however thrombogenicity shows charge dependence as described above for haemolysis. Specifically Koziara et al. have shown that the platelet aggregation and activation increases with increasing the particles surface charge and decreases with PEG coating(Koziara et al., 2005).

4.3 Complement activation

The biodistribution of intravenously administered nanocarriers can be affected by nanocarrier-induced complement activation in the form of rapid clearance from the systemic circulation via complement receptor-mediated phagocytosis by reticuloendothelial cells. In addition to its key role in nonspecific pathogen clearance, complement activation was confirmed to be essential in assisting cell-mediated immunity through improvement of B-cell responses to an antigen and elevation of the stimulation of dendritic cells (DC) and T-cells (Knopf et al., 2008). The

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 2127-2144 www.ijprajournal.com ISSN: 2249-7781

Complement activation in response to systemically administered drugs is answerable for hypersensitivity (allergic) reactions and anaphylaxis, a life-threatening condition. For itself, nano particulate carriers which are intended for systemic administration should be tested for the tendency to activate the complement system. If the nanocarrier does cause noteworthy complement activation, its surface characteristics must be modified to minimize these interactions to a tolerable level.

V. LONG CIRCULATING NANOCARRIERS

5.1 Pegylation

Prolongation of systemic circulation time is a common strategy to increase the retention time of the nanoparticles (NPs). Surface modification with coating of Polyethylene glycol (PEG) imparts stealthy characteristic to NPs, which prevent the binding of opsonins and avoid uptake by the reticulo-endothelial cells. Protein resistant surface of NCs characteristically presents the following molecular uniqueness: (i) They are hydrophilic. (ii) Theyinclude hydrogen-bond acceptors. (iii) They do not include hydrogen-bond donors. (iv) Their overall electrical charge is neutral (Holmlin et al., 2001).

5.1.1 Mechanism of action of the PEG coating

The hydrophilic PEG-based coatings significantly increase the blood circulation time of the nanocarriers. PEG considered as non-toxic and was approved by the Food and Drug Administration (FDA) for internal use in humans (Harris, 1985).The mechanism behind the extension of blood half-life of PEG coating is its hydrophilicity which is based upon the formation of sterically hindered, hydrophilic coating which repels the proteins or opsonins to bind on the surface of nanocarriers and subsequently avoid uptake by phagocytic cells (Blume and Cevc, 1993, Tan et al., 1993, Torchilinl and Papisov, 1994).Although, hydrophilicity was considered a paramount requirement, but hydrophilicity is not only sufficient to fulfil the surface requirement to set up long circulating nanocarriers. To be sure the dextran coated liposomes have shorter circulation time than PEG-coated ones (Pain et al., 1984), regardless of the more hydrophilic nature of dextran compared to PEG.Besides hydrophilicity the other factors that play a major role in opsonisation process is chain flexibility (Blume and Cevc, 1993, Torchilinl and Papisov, 1994), polymer corona thickness (Moghimi et al., 1993a, Stolnik et al., 1995),molecular weight of PEG derivatives (Leroux et al., 1995, Peracchia et al., 1999),density on the carrier surface and configuration (Jeon and Andrade, 1991, Tirosh et al., 1998, Du et al., 2001).

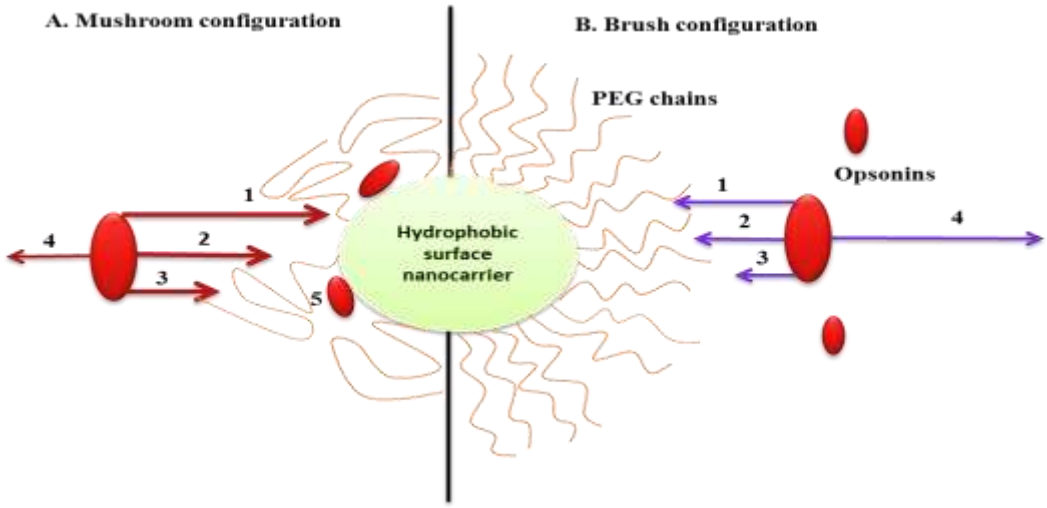

Fig. 3 Mechanism of interaction between opsonins and pegylated hydrophobic surface nanocarrier, in both brush and mushroom configuration of PEG chains 1: hydrophobic attraction force between the opsonin and hydrophobic surface nanocarrier, 2: Vander-waals attraction between the opsonin and hydrophobic surface nanocarrier, 3: Vander-waals attraction between the opsonin and PEG chains, 4: steric repulsion resulting from PEG chains, 5: minimum density of PEG chains results in opsonin adsorption on the hydrophobic surfaced nanocarrier.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 2127-2144 www.ijprajournal.com ISSN: 2249-7781

5.1.2 Chain Flexibility

Chain flexibility is another feature of PEG coated layer which play an important role in imparting stealth character to the intravenously administered particles other than hydrophilicity (Blume and Cevc, 1993, Torchilinl and Papisov, 1994).Due to the transient, flexible and rapidly changing structure of PEG chains the opsonin found difficulty in recognizing the surface for adsorption (Woodle and Lasic, 1992).The hydrophilicity and chain flexibility both serves as an effective coating protector for intravenously administered particles against opsonisation (Torchilinl and Papisov, 1994), hydrophilicity provides a sterically hindered hydrodynamic surface and flexibility is required for repelling proteins from polymer chains on particle surface yielding stealth nanocarrier (Shalaby, 1984).Accordingly, the lower complement activation of PEG as compared to dextran (Pain et al., 1984)may be due to the flexible nature of PEG molecules.

5.1.3Polymer layer thickness and molecular weight

The optimum layer thickness of PEG chains is required to avoid interaction of plasma proteins (opsonins) with the hydrophobic surface of particles. The minimum coating layer thickness that can guarantee efficient particle coating depends on a number of factors including the possible adsorbable proteins and the nanocarrier size (Rudt and Müller, 1992).Studies have revealed that a minimum effective hydrodynamic layer thickness is about 5% of the particle diameter (Stolnik et al., 1995).Moghimi et al. demonstrated that 4kDa PEG provide coating thickness of 5nm which found efficient protective layer for 60-200nm Polystyrene particles from complement activation and subsequent mono nuclear phagocytic uptake by macrophages (Moghimi et al., 1993b).Further several studies revealed that increasing the molecular weight of PEG proportionally the blood half-life of PEG coated nanocarriers increased(Leroux et al., 1995, Peracchia et al., 1999).

5.1.4Density on the carrier surface and configuration

The conditions that lead to protein repulsion from hydrophobic plane surfaces to which PEG chains were attached to one chain end in a "brush" configuration were recently studied (Jeon and Andrade, 1991).The best conditions for protein repulsion were found to be long PEG chain length and high surface density that is brush configuration (Jeon et al., 1991).The mushroom like structure is results from the low surface density of PEG molecules covering the surface of nanocarrier (Tirosh et al., 1998, Du et al., 2001)and at high PEG density, the PEG molecules extends in such a manner that avoid overlap with other PEG molecule thus resulting in brush configuration (Tirosh et al., 1998, Gref et al., 2000).The protective layer of PEG is considered as a cloud of possible chain confirmation with a high density enough to prevent interaction of opsonin with the surface of particles. In particular the PEG segments bound to the nanoparticles surface can form a large water cloud by linking two to three water molecule with each PEG molecule resulting in a brush or mushroom configuration and sterically repel the deposition of large proteins (Vonarbourg et al., 2006).The surface configuration of PEG coated nanocarriers can be determined by various techniques such as small angle neutrons cattering (Washington and King, 1997),measurement of ultrasound velocity and by measuring surface adsorbed proteins on the surface of nanocarriers (Gregoriadis, 1998).

5.2 Alternative approaches for long circulatory nanocarriers

5.2.1 Poloxamine and Poloxamer

From past several decades Surface modification by using poloxamer and poloxamine were utilized as one of the major approach to reduce the phagocytic uptake by the reticuloendothelial system after i.v. administration as it imparts hydration layer on the surface of nanocarriers. These are amphiphilic block copolymers comprising of hydrophilic blocks of ethylene oxide (EO) and hydrophobic blocks of propylene oxide (PO) monomer units. Poloxamers are a-b-a type triblock copolymers (PEO-PPO-PEO) whereas poloxamines are tetrablock copolymers of PEO-PPO linked through ethylenediamine bridges [(PEO-PPO)2–N–CH2–CH2–N–(PPO-PEO)2] (Yokoyama, 1991, Kumar et al., 2001, Adams et al., 2003).These polymers can be physically adsorbed on the nanocarrier surface through the hydrophobic PPO fraction. The hydrophobic PPO fraction adsorb physically on the hydrophobic surface of the nanocarrier exposing the hydrophilic fraction to the surface. Several research studies revealed that the coating obtained by poloxamine and poloxamer bestow hydrophilic coating and increase the retention time in systemic

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 2127-2144 www.ijprajournal.com ISSN: 2249-7781

circulation. Susan et al demonstrated that the surface modified PLGA nanoparticles having size ranges from 80-150 nm with polypropylene oxide-polyethylene oxide (PPO-PEO) block copolymers of the poloxamer and poloxamine series (poloxamer 407, poloxamine 904 and poloxamine 908) shows that poloxamer 407 or poloxamine 908 surface modified PLGA nanoparticles display prolonged blood circulation time accompanied by a combined lessening in liver and spleen accumulation after intravenous injection in the rat. Three hours post intravenous injection, 39% and 28% of the administered dose of poloxamer 407- and poloxamine 908-coated PLGA nanospheres remains in the blood circulation(Dunn et al., 1997).

5.2.2 Polysaccharides

The hydrophilic nature of polysaccharides makes them suitable for imparting stealth coating to nanocarriers in blood stream. Several research groups prepared the surface modified nanoparticles with derivatives of chitosan(Fan et al., 2010, Kim et al., 2010),dextran(Mehvar, 2000, Li et al., 2009),hyaluronic acid (Choi et al., 2010), and heparin(Park et al., 2007, Wang et al., 2009b, Ye et al., 2014)providing surface shielded hydrophilic layer on nanoparticle surface resulting in increased circulation half-life. Furthermore polysaccharides are biodegradable, biocompatible and less immunogenic and toxic and bearing multifunctional groups useful for ligand attachment and drug conjugation(Park et al., 2007, Kean and Thanou, 2010, Li et al., 2011).

Papisov et al projected to use acyclic hydrophilic polyacetals which is a derivative of polycarbohydrates to substitute PEG(Papisov, 2001).Hydrophilic polyacetal found to have parallel characters as PEG that is biodegradability and availability of freely modified functional groups 140. In addition, a polylysine grafted with polyacetal had considerably longer half-life as compared to polylysine grafted with dextran. Although polyacetal is derived from dextran, a new biocompatible polymer that can be prepare by reversibly modifying dextran with an acetal-shielded group(Bachelder et al., 2008).This dissimilarity was due to the removal of rigid stereospecific structures of dextran(Papisov, 2001).

5.2.3 Zwitterionic Polymers

Xio et al in 2012 developed a noval long circulatory blood pool contrast agent by introducing zwiterionic structure on the surface of polyacrylic acid coated magnetite nanoparticles(Xiao et al., 2012). Zwitterionic structure was made-up by 3-(diethylamino)propylamine (DEAPA). DEAPA grafting was done via EDC/NHS [N-(3-dimethylaminopropyl)-N'-ethylcarbo-diimide hydrochloride/N-hydroxysuccinimide] coupling chemistry. These particles showing five times lower macrophage cell uptake, longer circulation time and low cell toxicity than uncoated particles(Xiao et al., 2012). Further zwitterionic phospholipid derivatives have been confirmed to decrease the complement activation induced by liposomes (Vermette and Meagher, 2003).Likewise PEG, zwiterionic polymers bind water molecules strongly and form a electrostatically induced hydration layer (Chen et al., 2011)that decreases the rate of opsonin adsorption in blood stream. Betaines such as sulfobetaine and carboxybetaine are zwitterionic molecules, which bind water molecules via electrostatic interactions(Jiang and Cao, 2010, Shao et al., 2010), more strongly than those depend on hydrogen bonding like PEG (Chen et al., 2011).Therefore from the above evidences the zwiterionic polymers found comparable to that of commonly used poly-(ethylene glycol) (PEG) for imparting stealth character to intravenously administered nanocarriers.

5.2.4 Polyglycerols

Polyglycerols (PGs) or polyglycidols are biocompatible and flexible hydrophilic aliphatic polyether polyols, arranged in branched or linear forms, with an antifouling effect that is comparable to PEG (Siegers et al., 2004, Kainthan et al., 2006, Kainthan et al., 2007).In addition polyglycerols are hyperbranched contain multiple hydroxyl groups, that allows it for further functionalization(Siegers et al., 2004). Hyperbranced polyglycerols having long circulation half-lives of (33 hours for 106 kDa and 57 hours for 540 kDa) specify their potential as stealth polymers(Kainthan and Brooks, 2007). Liposome and gold decorated with PGs show minimum protein adsorption and extended blood circulation time(Maruyama et al., 1994, Siegers et al., 2004).

Wyszogrodzka et al in 2009 studied the interaction of biofouling relevant proteins: fibrinogen, lysozyme, albumin and pepsin with a series of hyperbranched polyglycerol dendrons modified by alkanethiols. The results demonstrated that the all polyglycerol dendrons possess excellent resistance to test proteins upto studied time frame of 24 hrs(Wyszogrodzka and Haag, 2009).

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 2127-2144 www.ijprajournal.com ISSN: 2249-7781

Hyperbranched polyglycerols resist the nonspecific adsorption of proteins on magnetic nanoparticles. The capability of hyperbranched polyglycerols is comparable favorably with the performance of methyloxy poly(ethylene glycol) (a linear mPEG with a molecular weight of 750) in resisting the adsorption of proteins(Wang et al., 2008).Moreover, PGs have greater resistance to heat and oxidative stress as compared to PEG, which makes them potential candidates for biomedical applications (Siegers et al., 2004).

5.2.5Polyoxazolines

Polyoxazoline (POx) have been extensively used as a hydrophilic segment in amphiphilic block-co-polymer. Poly (2-ethyl-2-oxazoline) make amphiphilic diblock polymer by coupling with a hydrophobic block polymer to form polymeric micells such as POx coupled with poly (epsilon-caprolactone)(Cheon Lee et al., 2003), poly(1,3-trimethylene carbonate)(Kim et al., 2000) and poly(aspartic acid)(Wang et al., 2009a). Moreover poly (2-ethyl-2-oxazoline) grafted with poly (L-lysine) was found a promising carrier as compared to PEG grafted poly (L-lysine) for the delivery of non-viral therapeutic DNA(von Erlach et al., 2011). In addition, POx was also used in a study to graft liposomes and shown to be comparable to PEG in prolonging the circulation time(Zalipsky et al., 1996). Recent study on cytotoxicity testing of poly(2-oxazoline) amphiphiles reveals that these polymers are typically not cytotoxic even at high concentrations(Luxenhofer et al., 2011).

5.2.6 Poly (amino acids)

Poly-(hydroxyethyl l-glutamine) and poly-(hydroxyethyl-l-asparagine) (PHEA) are two examples of poly-(amino acids) which have been developed as a substitute for PEG. These poly(amino acids) acts as potential stealth polymers (Metselaar et al., 2003) and gets degraded without difficulty, reducing the risk of accumulation and toxicity (Romberg et al., 2007a).Also these polymers prolong the blood circulation of NPs at par with PEG. Additionally PHEA coated liposomes proved to be more effective than PEGylated liposomes in maintaining the stealth effect of accelerated blood clearance at low lipid doses(Romberg et al., 2007b).

5.2.7 N-(2-hydroxypropyl)methacrylamide (HPMA)

First reported by Kopecek et al (Kopecek et al., 1973), HPMA brought a new era in macromolecular drug delivery as they possess varied properties such as biocompatibility, hydrophilicity and their ability to accommodate structural modifications (Lammers et al., 2009, Kopecek and Kopeckova, 2010). HPMA conjugated low molecular weight drugs and targeting moieties increases their circulation time which allows for EPR mediated tumor accumulation(Rihova et al., 1988, Rihova et al., 2001, Erez et al., 2009, Pike and Ghandehari, 2010). Drugs conjugated via an enzymatically cleavable peptide linker facilitates intracellular drug release (e.g., GFLG)(Rejmanová et al., 1983).

5.3 Biomimetic approaches

In last few decades interest is growing towards biomimetic coating for imparting stealth character to intravenously administered nanocarriers so that they will remain in systemic circulation for a prolong period of time.

5.3.1 RBC based nanocarriers

Recently, a new approach for producing biomimetic nanoparticles has been motivated by body's own long circulatory entities, red blood cells (RBCs). RBCs are natural carriers for oxygen having highly flexible structure with circulation half-life of 120 days, represents an ideal system for prolonging the circulation time of intravenously injected nanocarriers beyond that of pegylated nanocarriers(Fang et al., 2012). Doshi et al and markel et al developed highly concave nanoparticles and showed that mechanobiological mimicry of RBCs can increase the particle elasticity and extend their circulation time(Doshi et al., 2009, Merkel et al., 2011). Hu et al have developed a new drug delivery platform that couples RBC membrane derived vesicles with polymeric nanoparticles prepared from Poly (lactic-co-glycolic acid) (PLGA) polymer (Hu et al., 2011).

Furthermore finding of RBCs membrane proteins revealed that the RBC surface bound proteins helps to prevent their uptake by macrophages. For example, CD47 has been identified on RBC surface which prevent the uptake of RBCs by macrophages(Oldenborg et al., 2000).In addition to CD47, the other proteins identified on RBC surface including C8-binding proteins (C8bp)(Schönermark et al.,

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 2127-2144 www.ijprajournal.com ISSN: 2249-7781

1986),homologous restriction proteins (HRP)(Zalman et al., 1986), decay accelerating factor (DAF), membrane cofactor protein (MCP), complement receptor 1 (CR1) and CD59(Kim et al., 2008)prevent the recognition by the complement system thereby reducing their uptake. Tsai et al in 2010 developed CD47 surface conjugated polystyrene beads and characterized for macrophage uptake. It was found that CD47 conjugated polystyrene beads prevent the macrophage uptake(Tsai et al., 2010).

Thus the above findings gave the concept that if the delivery system possesses autologous surface characteristics to that of RBCs then such system might be able to make the delivery system long circulatory.

5.3.2 Biomimetic mucin

Mucins, a dominant class of large and heavily glycosylated proteins that is characterized by extended regions of densely clustered serine and threonine residues bearing O-linked glycans linked with N-acetyl galactosyl amine present in the mucus of the epithelium (Lindén et al., 2008, Rabuka et al., 2008).Mucin is amphiphilic in nature which render them to act like natural surfactant like the pluronics(Shi et al., 1999).Their natural origin, defensive role against pathogen and anti-fouling features facilitate positive host reactions, compatibility and controlled cellular interaction that suggest possible roles for mucin as biocompatible coatings for synthetic materials (Crouzier et al., 2012).

These functions when applied for the modification of nanoparticle surface leads to the covering of surface epitopes and thereby making the nanoparticle long circulating and non-immunogenic. Thasneem et al in 2013 prepared mucin functionalized Poly lactic-co-glycolic acid (PLGA) nanoparticles by conjugation of amino group of mucin to the terminal carboxylic acid groups on PLGA followed by nanoparticles synthesis via solvent evaporation method. The results revealed that the mucin modified PLGA nanoparticles proved promising in reducing the plasma protein (opsonin) adsorption and subsequent complement and platelet activation (Thasneem et al., 2013).

VI. CONCLUSION

Long circulating carrier system offers an excellent therapeutic strategy against systemic infections. Pegylation and bio-molecular approach seems to have a better therapeutic prospect among the various approach being exercised so far in this field. However the clinical effectiveness of these strategies requires a detail acute and chronic toxicological profiling of the system in blood. With the advent in molecular pharmacology and pharmaceutical technology we can understand better the molecular consequences of opsonisation process which helps in the development of an appropriate mechanism against systemic infections.

REFERENCE

[1]. ADAMS, M. L., LAVASANIFAR, A. & KWON, G. S. 2003. Amphiphilic block copolymers for drug delivery. Journal of pharmaceutical sciences, 92**,** 1343-1355.

[2]. AGASHE, H. B., DUTTA, T., GARG, M. & JAIN, N. 2006. Investigations on the toxicological profile of functionalized fifth-generation poly (propylene imine) dendrimer. Journal of Pharmacy and Pharmacology, 58**,** 1491-1498.

[3]. AGGARWAL, P., HALL, J. B., MCLELAND, C. B., DOBROVOLSKAIA, M. A. & MCNEIL, S. E. 2009. Nanoparticle interaction with plasma proteins as it relates to particle biodistribution, biocompatibility and therapeutic efficacy. Advanced Drug Delivery Reviews, 61**,** 428-437.

[4]. ALEXIS, F., PRIDGEN, E., MOLNAR, L. K. & FAROKHZAD, O. C. 2008. Factors affecting the clearance and biodistribution of polymeric nanoparticles. Molecular pharmaceutics, 5**,** 505-515.

[5]. ARVIZO, R. R., MIRANDA, O. R., MOYANO, D. F., WALDEN, C. A., GIRI, K., BHATTACHARYA, R., ROBERTSON, J. D., ROTELLO, V. M., REID, J. M. & MUKHERJEE, P. 2011. Modulating pharmacokinetics, tumor uptake and biodistribution by engineered nanoparticles. PloS one, 6**,** e24374.

[6]. BACHELDER, E. M., BEAUDETTE, T. T., BROADERS, K. E., DASHE, J. & FRÉCHET, J. M. 2008. Acetal-derivatized dextran: an acid-responsive biodegradable material for therapeutic applications. Journal of the American Chemical Society, 130**,** 10494-10495.

[7]. BERMEJO, J. F., ORTEGA, P., CHONCO, L., ERITJA, R., SAMANIEGO, R., MÜLLNER, M., DE JESUS, E., DE LA MATA, F. J., FLORES, J. C. & GOMEZ, R. 2007.

Water-Soluble Carbosilane Dendrimers: Synthesis Biocompatibility and Complexation with Oligonucleotides; Evaluation for Medical Applications. Chemistry-a European Journal, 13**,** 483-495.

[8]. BERTRAND, N. & LEROUX, J.-C. 2012. The journey of a drug-carrier in the body: an anatomo-physiological perspective. Journal of controlled release, 161**,** 152-163.

[9]. BLUME, G. & CEVC, G. 1993. Molecular mechanism of the lipid vesicle longevity in vivo. Biochimica et Biophysica Acta (BBA)-Biomembranes, 1146**,** 157-168.

[10]. CAMPBELL, R. B., FUKUMURA, D., BROWN, E. B., MAZZOLA, L. M., IZUMI, Y., JAIN, R. K., TORCHILIN, V. P. & MUNN, L. L. 2002. Cationic charge determines the distribution of liposomes between the vascular and extravascular compartments of tumors. Cancer Research, 62**,** 6831-6836.

[11]. CARRSTENSEN, H., MÜLLER, R. & MÜLLER, B. 1992. Particle size, surface hydrophobicity and interaction with serum of parenteral fat emulsions and model drug carriers as parameters related to RES uptake. Clinical nutrition, 11**,** 289-297.

[12]. CHAMPION, J. A. & MITRAGOTRI, S. 2006. Role of target geometry in phagocytosis. Proceedings of the National Academy of Sciences of the United States of America, 103**,** 4930-4934.

[13]. CHAUHAN, V. P., POPOVIĆ, Z., CHEN, O., CUI, J., FUKUMURA, D., BAWENDI, M. G. & JAIN, R. K. 2011. Fluorescent Nanorods and Nanospheres for Real-Time In Vivo Probing of Nanoparticle Shape-Dependent Tumor Penetration. Angewandte Chemie, 123**,** 11619-11622.

[14]. CHEN, S., CHEN, S., JIANG, S., MO, Y., LUO, J., TANG, J. & GE, Z. 2011. Study of zwitterionic sulfopropylbetaine containing reactive siloxanes for application in antibacterial materials. Colloids and Surfaces B: Biointerfaces, 85**,** 323-329.

[15]. CHEON LEE, S., KIM, C., CHAN KWON, I., CHUNG, H. & YOUNG JEONG, S. 2003. Polymeric micelles of poly(2-ethyl-2-oxazoline)-block-poly(epsilon-caprolactone) copolymer as a carrier for paclitaxel. J Control Release, 89**,** 437-46.

[16]. CHOI, H. S., LIU, W., MISRA, P., TANAKA, E., ZIMMER, J. P., IPE, B. I., BAWENDI, M. G. & FRANGIONI, J. V. 2007. Renal clearance of quantum dots. Nature biotechnology, 25**,** 1165-1170.

[17]. CHOI, K. Y., CHUNG, H., MIN, K. H., YOON, H. Y., KIM, K., PARK, J. H., KWON, I. C. & JEONG, S. Y. 2010. Self-assembled hyaluronic acid nanoparticles for active tumor targeting. Biomaterials, 31**,** 106-114.

[18]. CROUZIER, T., BECKWITT, C. H. & RIBBECK, K. 2012. Mucin Multilayers Assembled through Sugar–Lectin Interactions. Biomacromolecules, 13**,** 3401-3408.

[19]. DOBROVOLSKAIA, M. A., AGGARWAL, P., HALL, J. B. & MCNEIL, S. E. 2008. Preclinical studies to understand nanoparticle interaction with the immune system and its potential effects on nanoparticle biodistribution. Molecular pharmaceutics, 5**,** 487-495.

[20]. DOBROVOLSKAIA, M. A. & MCNEIL, S. E. 2007. Immunological properties of engineered nanomaterials. Nature nanotechnology, 2**,** 469-478.

[21]. DOMAŃSKI, D., KLAJNERT, B. & BRYSZEWSKA, M. 2004. Influence of PAMAM dendrimers on human red blood cells. Bioelectrochemistry, 63**,** 189-191.

[22]. DOSHI, N., ZAHR, A. S., BHASKAR, S., LAHANN, J. & MITRAGOTRI, S. 2009. Red blood cell-mimicking synthetic biomaterial particles. Proceedings of the National Academy of Sciences, 106**,** 21495-21499.

[23]. DU, H., SCHIAVI, S., LEVINE, M., MISHRA, J., HEUR, M. & GRABOWSKI, G. A. 2001. Enzyme therapy for lysosomal acid lipase deficiency in the mouse. Human molecular genetics, 10**,** 1639-1648.

[24]. DUNN, S. E., COOMBES, A. G., GARNETT, M. C., DAVIS, S. S., DAVIES, M. C. & ILLUM, L. 1997. In vitro cell interaction and in vivo biodistribution of poly (lactide-co-glycolide) nanospheres surface modified by poloxamer and poloxamine

copolymers. Journal of controlled release, 44**,** 65-76.

[25]. DUTTA, T., AGASHE, H. B., GARG, M., BALASUBRAMANIUM, P., KABRA, M. & JAIN, N. K. 2007. Poly (propyleneimine) dendrimer based nanocontainers for targeting of efavirenz to human monocytes/macrophages in vitro: Research Paper. Journal of drug targeting, 15**,** 89-98.

[26]. EREZ, R., SEGAL, E., MILLER, K., SATCHI-FAINARO, R. & SHABAT, D. 2009. Enhanced cytotoxicity of a polymer-drug conjugate with triple payload of paclitaxel. Bioorg Med Chem, 17**,** 4327-35.

[27]. FAN, L., LI, F., ZHANG, H., WANG, Y., CHENG, C., LI, X., GU, C.-H., YANG, Q., WU, H. & ZHANG, S. 2010. Co-delivery of PDTC and doxorubicin by multifunctional micellar nanoparticles to achieve active targeted drug delivery and overcome multidrug resistance. Biomaterials, 31**,** 5634-5642.

[28]. FANG, R. H., HU, C.-M. J. & ZHANG, L. 2012. Nanoparticles disguised as red blood cells to evade the immune system. Expert Opinion on Biological Therapy, 12**,** 385-389.

[29]. FOX, M. E., SZOKA, F. C. & FRÉCHET, J. M. 2009. Soluble polymer carriers for the treatment of cancer: the importance of molecular architecture. Accounts of chemical research, 42**,** 1141-1151.

[30]. FRANK, M. M. & FRIES, L. F. 1991. The role of complement in inflammation and phagocytosis. Immunology today, 12**,** 322-326.

[31]. GREF, R., LÜCK, M., QUELLEC, P., MARCHAND, M., DELLACHERIE, E., HARNISCH, S., BLUNK, T. & MÜLLER, R. 2000. 'Stealth'corona-core nanoparticles surface modified by polyethylene glycol (PEG): influences of the corona (PEG chain length and surface density) and of the core composition on phagocytic uptake and plasma protein adsorption. Colloids and Surfaces B: Biointerfaces, 18**,** 301-313.

[32]. GREGORIADIS, G. 1998. Targeting of drugs 6: strategies for stealth therapeutic systems, Springer.

[33]. HARRIS, J. M. 1985. Laboratory synthesis of polyethylene glycol derivatives. Journal of Macromolecular Science-Reviews in Macromolecular Chemistry and Physics, 25**,** 325-373.

[34]. HE, C., HU, Y., YIN, L., TANG, C. & YIN, C. 2010. Effects of particle size and surface charge on cellular uptake and biodistribution of polymeric nanoparticles. Biomaterials, 31**,** 3657-3666.

[35]. HOLMLIN, R. E., CHEN, X., CHAPMAN, R. G., TAKAYAMA, S. & WHITESIDES, G. M. 2001. Zwitterionic SAMs that resist nonspecific adsorption of protein from aqueous buffer. Langmuir, 17**,** 2841-2850.

[36]. HU, C.-M. J., ZHANG, L., ARYAL, S., CHEUNG, C., FANG, R. H. & ZHANG, L. 2011. Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform. Proceedings of the National Academy of Sciences, 108**,** 10980-10985.

[37]. ILIUM, L., HUNNEYBALL, I. & DAVIS, S. 1986. The effect of hydrophilic coatings on the uptake of colloidal particles by the liver and by peritoneal macrophages. International journal of pharmaceutics, 29**,** 53-65.

[38]. JANÁT-AMSBURY, M., RAY, A., PETERSON, C. & GHANDEHARI, H. 2011. Geometry and surface characteristics of gold nanoparticles influence their biodistribution and uptake by macrophages. European journal of pharmaceutics and biopharmaceutics, 77**,** 417-423.

[39]. JEON, S. & ANDRADE, J. 1991. Protein—surface interactions in the presence of polyethylene oxide: II. Effect of protein size. Journal of colloid and interface science, 142**,** 159-166.

[40]. JEON, S., LEE, J., ANDRADE, J. & DE GENNES, P. 1991. Protein—surface interactions in the presence of polyethylene oxide: I. Simplified theory. Journal of colloid and interface science, 142**,** 149-158.

[41]. JIANG, S. & CAO, Z. 2010. Ultralow-Fouling, Functionalizable, and Hydrolyzable Zwitterionic Materials and Their Derivatives for Biological Applications. Advanced Materials, 22**,** 920-932.

[42]. JOHNSON, R. 2004. The complement system. Ratner, BD, Hoffman, AS, Schoen, FJ.
[43]. KAINTHAN, R. K. & BROOKS, D. E. 2007. < i> In vivo</i> biological evaluation of high molecular weight hyperbranched polyglycerols. Biomaterials, 28**,** 4779-4787.
[44]. KAINTHAN, R. K., HESTER, S. R., LEVIN, E., DEVINE, D. V. & BROOKS, D. E. 2007. < i> In vitro</i> biological evaluation of high molecular weight hyperbranched polyglycerols. Biomaterials, 28**,** 4581-4590.
[45]. KAINTHAN, R. K., JANZEN, J., LEVIN, E., DEVINE, D. V. & BROOKS, D. E. 2006. Biocompatibility testing of branched and linear polyglycidol. Biomacromolecules, 7**,** 703-709.
[46]. KEAN, T. & THANOU, M. 2010. Biodegradation, biodistribution and toxicity of chitosan. Advanced Drug Delivery Reviews, 62**,** 3-11.
[47]. KIM, C., LEE, S. C., SHIN, J. H., YOON, J.-S., KWON, I. C. & JEONG, S. Y. 2000. Amphiphilic diblock copolymers based on poly (2-ethyl-2-oxazoline) and poly (1, 3-trimethylene carbonate): synthesis and micellar characteristics. Macromolecules, 33**,** 7448-7452.
[48]. KIM, D. D., MIWA, T., KIMURA, Y., SCHWENDENER, R. A., VAN LOOKEREN CAMPAGNE, M. & SONG, W.-C. 2008. Deficiency of decay-accelerating factor and complement receptor 1–related gene/protein y on murine platelets leads to complement-dependent clearance by the macrophage phagocytic receptor CRIg. Blood, 112**,** 1109-1119.
[49]. KIM, K., KIM, J. H., PARK, H., KIM, Y.-S., PARK, K., NAM, H., LEE, S., PARK, J. H., PARK, R.-W. & KIM, I.-S. 2010. Tumor-homing multifunctional nanoparticles for cancer theragnosis: simultaneous diagnosis, drug delivery, and therapeutic monitoring. Journal of controlled release, 146**,** 219-227.
[50]. KNOPF, P. M., RIVERA, D. S., HAI, S.-H., MCMURRY, J., MARTIN, W. & DE GROOT, A. S. 2008. Novel function of complement C3d as an autologous helper T-cell target. Immunology and cell biology, 86**,** 221-225.
[51]. KOHANE, D. S. & LANGER, R. 2010. Biocompatibility and drug delivery systems. Chem. Sci., 1**,** 441-446.
[52]. KOPECEK, J. & KOPECKOVA, P. 2010. HPMA copolymers: origins, early developments, present, and future. Adv Drug Deliv Rev, 62**,** 122-49.
[53]. KOPECEK, J., SPRINCL, L. & LIM, D. 1973. New types of synthetic infusion solutions. I. Investigation of the effect of solutions of some hydrophilic polymers on blood. J Biomed Mater Res, 7**,** 179-91.
[54]. KOTAGIRI, N., LEE, J. S. & KIM, J.-W. 2013. Selective pathogen targeting and macrophage evading carbon nanotubes through dextran sulfate coating and PEGylation for photothermal theranostics. Journal of Biomedical Nanotechnology, 9**,** 1008-1016.
[55]. KOZIARA, J., OH, J., AKERS, W., FERRARIS, S. & MUMPER, R. 2005. Blood compatibility of cetyl alcohol/polysorbate-based nanoparticles. Pharmaceutical research, 22**,** 1821-1828.
[56]. KUMAR, N., RAVIKUMAR, M. N. & DOMB, A. 2001. Biodegradable block copolymers. Advanced Drug Delivery Reviews, 53**,** 23-44.
[57]. LAMMERS, T., SUBR, V., ULBRICH, K., PESCHKE, P., HUBER, P. E., HENNINK, W. E. & STORM, G. 2009. Simultaneous delivery of doxorubicin and gemcitabine to tumors in vivo using prototypic polymeric drug carriers. Biomaterials, 30**,** 3466-75.
[58]. LEROUX, J. C., DE JAEGHERE, F., ANNER, B., DOELKER, E. & GURNY, R. 1995. An investigation on the role of plasma and serum opsonins on the internalization of biodegradable poly(D,L-lactic acid) nanoparticles by human monocytes. Life Sci, 57**,** 695-703.
[59]. LEVCHENKO, T. S., RAMMOHAN, R., LUKYANOV, A. N., WHITEMAN, K. R. & TORCHILIN, V. P. 2002. Liposome clearance in mice: the effect of a separate and combined presence of surface charge and polymer coating. International journal of pharmaceutics, 240**,** 95-102.
[60]. LI, H., NIU, R., YANG, J., NIE, J. & YANG, D. 2011. Photocrosslinkable tissue adhesive based on dextran. Carbohydrate Polymers, 86**,** 1578-1585.

[61]. LI, Y. L., ZHU, L., LIU, Z., CHENG, R., MENG, F., CUI, J. H., JI, S. J. & ZHONG, Z. 2009. Reversibly stabilized multifunctional dextran nanoparticles efficiently deliver doxorubicin into the nuclei of cancer cells. Angewandte Chemie International Edition, 48**,** 9914-9918.

[62]. LINDÉN, S. K., FLORIN, T. H. & MCGUCKIN, M. A. 2008. Mucin dynamics in intestinal bacterial infection. PloS one, 3**,** e3952.

[63]. LUXENHOFER, R., SAHAY, G., SCHULZ, A., ALAKHOVA, D., BRONICH, T. K., JORDAN, R. & KABANOV, A. V. 2011. Structure-property relationship in cytotoxicity and cell uptake of poly (2-oxazoline) amphiphiles. Journal of controlled release, 153**,** 73-82.

[64]. MAEDA, H. 1994. Polymer conjugated macromolecular drugs for tumor-specific targeting. Polymeric Site-Specific Pharmacotherapy**,** 95-116.

[65]. MALIK, A. N., WIWATTANAPATAPEE, R., KLOPSCH, R., LORENZ, K., FREY, H., WEENER, J., MEIJER, E., PAULUS, W. & DUNCAN, R. 2000. Dendrimers:: Relationship between structure and biocompatibility in vitro, and preliminary studies on the biodistribution of 125I-labelled polyamidoamine dendrimers in vivo. Journal of controlled release, 65**,** 133-148.

[66]. MARUYAMA, K., OKUIZUMI, S., ISHIDA, O., YAMAUCHI, H., KIKUCHI, H. & IWATSURU, M. 1994. Phosphatidyl polyglycerols prolong liposome circulation in vivo. International journal of pharmaceutics, 111**,** 103-107.

[67]. MEHVAR, R. 2000. Dextrans for targeted and sustained delivery of therapeutic and imaging agents. Journal of controlled release, 69**,** 1-25.

[68]. MERKEL, T. J., JONES, S. W., HERLIHY, K. P., KERSEY, F. R., SHIELDS, A. R., NAPIER, M., LUFT, J. C., WU, H., ZAMBONI, W. C. & WANG, A. Z. 2011. Using mechanobiological mimicry of red blood cells to extend circulation times of hydrogel microparticles. Proceedings of the National Academy of Sciences, 108**,** 586-591.

[69]. METSELAAR, J. M., BRUIN, P., DE BOER, L. W., DE VRINGER, T., SNEL, C., OUSSOREN, C., WAUBEN, M. H., CROMMELIN, D. J., STORM, G. & HENNINK, W. E. 2003. A novel family of L-amino acid-based biodegradable polymer-lipid conjugates for the development of long-circulating liposomes with effective drug-targeting capacity. Bioconjug Chem, 14**,** 1156-64.

[70]. MITCHELL, R. 2004. Innate and adaptive immunity: the immune response to foreign materials. Biomaterials Science: An Introduction to Materials in Medicine. Elsevier Academic Press, Amsterdam**,** 304-318.

[71]. MOGHIMI, S. M., HEDEMAN, H., MUIR, I., ILLUM, L. & DAVIS, S. S. 1993a. An investigation of the filtration capacity and the fate of large filtered sterically-stabilized microspheres in rat spleen. Biochimica et Biophysica Acta (BBA)-General Subjects, 1157**,** 233-240.

[72]. MOGHIMI, S. M., MUIR, I., ILLUM, L., DAVIS, S. S. & KOLB-BACHOFEN, V. 1993b. Coating particles with a block co-polymer (poloxamine-908) suppresses opsonization but permits the activity of dysopsonins in the serum. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1179**,** 157-165.

[73]. MOVAT, H. Z., WEISER, W. J., GLYNN, M. F. & MUSTARD, J. F. 1965. Platelet phagocytosis and aggregation. The Journal of cell biology, 27**,** 531-543.

[74]. NEUN, B. W. & DOBROVOLSKAIA, M. A. 2011. Method for in vitro analysis of nanoparticle thrombogenic properties. Characterization of Nanoparticles Intended for Drug Delivery. Springer.

[75]. NORMAN, M., WILLIAMS, P. & ILLUM, L. 1992. Human serum albumin as a probe for surface conditioning (opsonization) of block copolymer-coated microspheres. Biomaterials, 13**,** 841-849.

[76]. OLDENBORG, P.-A., ZHELEZNYAK, A., FANG, Y.-F., LAGENAUR, C. F., GRESHAM, H. D. & LINDBERG, F. P. 2000. Role of CD47 as a marker of self on red blood cells. Science, 288**,** 2051-2054.

[77]. OWENS III, D. E. & PEPPAS, N. A. 2006. Opsonization, biodistribution, and

pharmacokinetics of polymeric nanoparticles. International journal of pharmaceutics, 307**,** 93-102.

[78]. PAIN, D., DAS, P., GHOSH, P. & BACHHAWAT, B. 1984. Increased circulatory half-life of liposomes after conjunction with dextran. Journal of Biosciences, 6**,** 811-816.

[79]. PAPISOV, M. Acyclic Polyacetals from Polysaccharides: Biomimetic Biomedical" Stealth" Polymers. ACS Symposium Series, 2001. Washington, DC; American Chemical Society; 1999, 301-315.

[80]. PARK, K., KI LEE, S., HYUN SON, D., AH PARK, S., KIM, K., WON CHANG, H., JEONG, E.-J., PARK, R.-W., KIM, I.-S. & CHAN KWON, I. 2007. The attenuation of experimental lung metastasis by a bile acid acylated-heparin derivative. Biomaterials, 28**,** 2667-2676.

[81]. PASSIRANI, C., BARRATT, G., DEVISSAGUET, J.-P. & LABARRE, D. 1998. Long-circulating nanopartides bearing heparin or dextran covalently bound to poly (methyl methacrylate). Pharmaceutical research, 15**,** 1046-1050.

[82]. PERACCHIA, M., FATTAL, E., DESMAELE, D., BESNARD, M., NOEL, J., GOMIS, J., APPEL, M., D'ANGELO, J. & COUVREUR, P. 1999. Stealth< sup>®</sup> PEGylated polycyanoacrylate nanoparticles for intravenous administration and splenic targeting. Journal of controlled release, 60**,** 121-128.

[83]. PIKE, D. B. & GHANDEHARI, H. 2010. HPMA copolymer-cyclic RGD conjugates for tumor targeting. Adv Drug Deliv Rev, 62**,** 167-83.

[84]. PLARD, J.-P. & BAZILE, D. 1999. Comparison of the safety profiles of PLA< sub> 50</sub> and Me. PEG-PLA< sub> 50</sub> nanoparticles after single dose intravenous administration to rat. Colloids and Surfaces B: Biointerfaces, 16**,** 173-183.

[85]. RABUKA, D., FORSTNER, M. B., GROVES, J. T. & BERTOZZI, C. R. 2008. Noncovalent cell surface engineering: incorporation of bioactive synthetic glycopolymers into cellular membranes. Journal of the American Chemical Society, 130**,** 5947-5953.

[86]. RATNER, B. D., HOFFMAN, A. S., SCHOEN, F. & LEMONS, J. E. 2004. Biomaterials science: an introduction to materials in medicine. San Diego, California**,** 162-164.

[87]. REJMANOVÁ, P., KOPEČEK, J., POHL, J., BAUDYŠ, M. & KOSTKA, V. 1983. Polymers containing enzymatically degradable bonds, 8. Degradation of oligopeptide sequences in N-(2-hydroxypropyl) methacrylamide copolymers by bovine spleen cathepsin B. Die Makromolekulare Chemie, 184**,** 2009-2020.

[88]. RIHOVA, B., ETRYCH, T., PECHAR, M., JELINKOVA, M., STASTNY, M., HOVORKA, O., KOVAR, M. & ULBRICH, K. 2001. Doxorubicin bound to a HPMA copolymer carrier through hydrazone bond is effective also in a cancer cell line with a limited content of lysosomes. J Control Release, 74**,** 225-32.

[89]. RIHOVA, B., KOPECKOVA, P., STROHALM, J., ROSSMANN, P., VETVICKA, V. & KOPECEK, J. 1988. Antibody-directed affinity therapy applied to the immune system: in vivo effectiveness and limited toxicity of daunomycin conjugated to HPMA copolymers and targeting antibody. Clin Immunol Immunopathol, 46**,** 100-14.

[90]. ROMBERG, B., METSELAAR, J. M., BARANYI, L., SNEL, C. J., BUNGER, R., HENNINK, W. E., SZEBENI, J. & STORM, G. 2007a. Poly(amino acid)s: promising enzymatically degradable stealth coatings for liposomes. Int J Pharm, 331**,** 186-9.

[91]. ROMBERG, B., OUSSOREN, C., SNEL, C. J., CARSTENS, M. G., HENNINK, W. E. & STORM, G. 2007b. Pharmacokinetics of poly(hydroxyethyl-l-asparagine)-coated liposomes is superior over that of PEG-coated liposomes at low lipid dose and upon repeated administration. Biochim Biophys Acta, 1768**,** 737-43.

[92]. ROSER, M., FISCHER, D. & KISSEL, T. 1998. 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, 46**,** 255-263.

[93]. RUDT, S. & MÜLLER, R. 1992. In vitro phagocytosis assay of nano-and microparticles by chemiluminescence. I. Effect of analytical parameters, particle size and particle concentration. Journal of controlled release, 22**,** 263-271.

[94]. SAHAY, G., ALAKHOVA, D. Y. & KABANOV, A. V. 2010. Endocytosis of nanomedicines. Journal of controlled release, 145**,** 182-195.

[95]. SAHU, A. & LAMBRIS, J. D. 2001. Structure and biology of complement protein C3, a connecting link between innate and acquired immunity. Immunological reviews, 180**,** 35-48.

[96]. SALVADOR-MORALES, C., ZHANG, L., LANGER, R. & FAROKHZAD, O. C. 2009. Immunocompatibility properties of lipid–polymer hybrid nanoparticles with heterogeneous surface functional groups. Biomaterials, 30**,** 2231-2240.

[97]. SCHÖNERMARK, S., RAUTERBERG, E., SHIN, M., LÖKE, S., ROELCKE, D. & HÄNSCH, G. 1986. Homologous species restriction in lysis of human erythrocytes: a membrane-derived protein with C8-binding capacity functions as an inhibitor. The Journal of Immunology, 136**,** 1772-1776.

[98]. SHAH, D. S., SAKTHIVEL, T., TOTH, I., FLORENCE, A. T. & WILDERSPIN, A. F. 2000. DNA transfection and transfected cell viability using amphipathic asymmetric dendrimers. International journal of pharmaceutics, 208**,** 41-48.

[99]. SHALABY, S. W. 1984. Polymers as biomaterials, Plenum Publishing Corporation.

[100]. SHAO, Q., HE, Y., WHITE, A. D. & JIANG, S. 2010. Difference in hydration between carboxybetaine and sulfobetaine. The Journal of Physical Chemistry B, 114**,** 16625-16631.

[101]. SHARMA, G., VALENTA, D. T., ALTMAN, Y., HARVEY, S., XIE, H., MITRAGOTRI, S. & SMITH, J. W. 2010. Polymer particle shape independently influences binding and internalization by macrophages. Journal of controlled release, 147**,** 408-412.

[102]. SHENG, Y., LIU, C., YUAN, Y., TAO, X., YANG, F., SHAN, X., ZHOU, H. & XU, F. 2009. Long-circulating polymeric nanoparticles bearing a combinatorial coating of PEG and water-soluble chitosan. Biomaterials, 30**,** 2340-2348.

[103]. SHI, L., MILLER, C., CALDWELL, K. D. & VALINT, P. 1999. Effects of mucin addition on the stability of oil–water emulsions. Colloids and Surfaces B: Biointerfaces, 15**,** 303-312.

[104]. SIEGERS, C., BIESALSKI, M. & HAAG, R. 2004. Self-Assembled Monolayers of Dendritic Polyglycerol Derivatives on Gold That Resist the Adsorption of Proteins. Chemistry-a European Journal, 10**,** 2831-2838.

[105]. SINGER, L., COLTEN, H. & WETSEL, R. 1994. Complement C3 deficiency: human, animal, and experimental models. Pathobiology, 62**,** 14-28.

[106]. STOLNIK, S., ILLUM, L. & DAVIS, S. 1995. Long circulating microparticulate drug carriers. Advanced Drug Delivery Reviews, 16**,** 195-214.

[107]. TAN, J., BUTTERFIELD, D., VOYCHECK, C., CALDWELL, K. & LI, J. 1993. Surface modification of nanoparticles by PEO/PPO block copolymers to minimize interactions with blood components and prolong blood circulation in rats. Biomaterials, 14**,** 823-833.

[108]. THASNEEM, Y., REKHA, M., SAJEESH, S. & SHARMA, C. P. 2013. Biomimetic mucin modified PLGA nanoparticles for enhanced blood compatibility. Journal of colloid and interface science, 409**,** 237-244.

[109]. TIROSH, O., BARENHOLZ, Y., KATZHENDLER, J. & PRIEV, A. 1998. Hydration of polyethylene glycol-grafted liposomes. Biophysical journal, 74**,** 1371-1379.

[110]. TORCHILINL, V. & PAPISOV, M. 1994. Why do polyethylene glycol-coated liposomes circulate so long?: Molecular mechanism of liposome steric protection with polyethylene glycol: Role of polymer chain flexibility. Journal of liposome research, 4**,** 725-739.

[111]. TSAI, R. K., RODRIGUEZ, P. L. & DISCHER, D. E. 2010. Self inhibition of phagocytosis: The affinity of 'marker of self'CD47 for SIRPα dictates potency of inhibition but only at low expression

levels. Blood Cells, Molecules, and Diseases, 45**,** 67-74.

[112]. VERMETTE, P. & MEAGHER, L. 2003. Interactions of phospholipid-and poly (ethylene glycol)-modified surfaces with biological systems: relation to physico-chemical properties and mechanisms. Colloids and Surfaces B: Biointerfaces, 28**,** 153-198.

[113]. VINOGRADOV, S. V., BRONICH, T. K. & KABANOV, A. V. 2002. Nanosized cationic hydrogels for drug delivery: preparation, properties and interactions with cells. Advanced Drug Delivery Reviews, 54**,** 135-147.

[114]. VON ERLACH, T., ZWICKER, S., PIDHATIKA, B., KONRADI, R., TEXTOR, M., HALL, H. & LÜHMANN, T. 2011. Formation and characterization of DNA-polymer-condensates based on poly (2-methyl-2-oxazoline) grafted poly (l-lysine) for non-viral delivery of therapeutic DNA. Biomaterials, 32**,** 5291-5303.

[115]. VONARBOURG, A., PASSIRANI, C., SAULNIER, P. & BENOIT, J.-P. 2006. Parameters influencing the stealthiness of colloidal drug delivery systems. Biomaterials, 27**,** 4356-4373.

[116]. WANG, C.-H., WANG, W.-T. & HSIUE, G.-H. 2009a. Development of polyion complex micelles for encapsulating and delivering amphotericin B. Biomaterials, 30**,** 3352-3358.

[117]. WANG, S., ZHOU, Y., YANG, S. & DING, B. 2008. Growing hyperbranched polyglycerols on magnetic nanoparticles to resist nonspecific adsorption of proteins. Colloids and Surfaces B: Biointerfaces, 67**,** 122-126.

[118]. WANG, Y., XIN, D., HU, J., LIU, K., PAN, J. & XIANG, J. 2009b. A model ternary heparin conjugate by direct covalent bond strategy applied to drug delivery system. Bioorganic & medicinal chemistry letters, 19**,** 149-152.

[119]. WASHINGTON, C. & KING, S. 1997. Effect of electrolytes and temperature on the structure of a poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) block copolymer adsorbed to a perfluorocarbon emulsion. Langmuir, 13**,** 4545-4550.

[120]. WEI, A., MEHTALA, J. G. & PATRI, A. K. 2012. Challenges and opportunities in the advancement of nanomedicines. Journal of controlled release, 164**,** 236-246.

[121]. WOODLE, M. C. & LASIC, D. D. 1992. Sterically stabilized liposomes. Biochimica et Biophysica Acta (BBA)-Reviews on Biomembranes, 1113**,** 171-199.

[122]. WYSZOGRODZKA, M. & HAAG, R. 2009. Synthesis and characterization of glycerol dendrons, self-assembled monolayers on gold: a detailed study of their protein resistance. Biomacromolecules, 10**,** 1043-1054.

[123]. XIAO, K., LI, Y., LUO, J., LEE, J. S., XIAO, W., GONIK, A. M., AGARWAL, R. G. & LAM, K. S. 2011. The effect of surface charge on< i> in vivo</i> biodistribution of PEG-oligocholic acid based micellar nanoparticles. Biomaterials, 32**,** 3435-3446.

[124]. XIAO, W., LIN, J., LI, M., MA, Y., CHEN, Y., ZHANG, C., LI, D. & GU, H. 2012. Prolonged in vivo circulation time by zwitterionic modification of magnetite nanoparticles for blood pool contrast agents. Contrast media & molecular imaging, 7**,** 320-327.

[125]. YADAV, K. S., JACOB, S., SACHDEVA, G., CHUTTANI, K., MISHRA, A. K. & SAWANT, K. K. 2011. Long circulating PEGylated PLGA nanoparticles of cytarabine for targeting leukemia. Journal of microencapsulation, 28**,** 729-742.

[126]. YAMAMOTO, Y., NAGASAKI, Y., KATO, Y., SUGIYAMA, Y. & KATAOKA, K. 2001. Long-circulating poly (ethylene glycol)–poly (d, l-lactide) block copolymer micelles with modulated surface charge. Journal of controlled release, 77**,** 27-38.

[127]. YE, L., GAO, Z., ZHOU, Y., YIN, X., ZHANG, X., ZHANG, A. & FENG, Z. 2014. A pH-sensitive binary drug delivery system based on poly (caprolactone)–heparin conjugates. Journal of Biomedical Materials Research Part A, 102**,** 880-889.

[128]. YOKOYAMA, M. 1991. Block copolymers as drug carriers. Critical reviews in therapeutic drug carrier systems, 9**,** 213-248.

[129]. ZALIPSKY, S., HANSEN, C. B., OAKS, J. M. & ALLEN, T. M. 1996. Evaluation of blood clearance rates and biodistribution of poly (2-oxazoline)-grafted liposomes. Journal of pharmaceutical sciences, 85**,** 133-137.

[130]. ZALMAN, L. S., WOOD, L. M. & MÜLLER-EBERHARD, H. J. 1986. Isolation of a human erythrocyte membrane protein capable of inhibiting expression of homologous complement transmembrane channels. Proceedings of the National Academy of Sciences, 83**,** 6975-6979.