Chapter 14
Surface Modification Strategies in Enhancing Systemic Delivery Performance

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Abstract In Chap. 13, electrospinning has been introduced as a strategy to manipulate the physical properties of a therapeutics-loaded system and to enhance the versatility of drug delivery. In the remaining chapters in Section V, the use of chemical means to manipulate the surface properties of a carrier for more effective systemic drug delivery will be discussed. As a matter of fact, a therapeutic agent must stay in the body as long as it is needed to reach the intended site of action in order to elicit a therapeutic response. To extend the blood retention time of an agent, one commonly used strategy is surface modification. In this chapter, we will first discuss the principles of clearance of particulate drug delivery systems from the body by the mononuclear phagocyte system (MPS), followed by a discussion of the possible use of polymers as modifiers of the surface properties of the particulate systems for enhanced performance in systemic drug delivery. Finally, the applications of surface-modified particulates in non-MPS targeting, including cancer chemotherapy and delivery across the blood–brain barrier, will also be discussed.

Keywords Particle uptake · Mononuclear phagocyte system (MPS) · Opsonization · Surface modification · Multidrug resistance · Blood–brain barrier · Non-MPS targeting

14.1 Introduction

Particulate drug delivery systems occupy a key role in present day pharmaceutical and cosmetic products (Al Jamal and Kostarelos 2011; Lai and Shum 2016; Lai 2016). Despite their presence in pharmaceutical practice for quite some time, particulate systems are not popular as injectables, except for a few types of insulins. **Liposomes** are the first particulate system to be used as parenteral products (Al Jamal and Kostarelos 2011). It took about 30 years of research for liposomes to become commercially available. Surface-modified particulate systems are particulates with

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altered surface properties to specifically act for a definite purpose; for the realm of this chapter, it is primarily the modification of the mononuclear phagocyte system (MPS) recognition and thereby provides a modified disposition in the body.

Surface-modified particles are mainly used for: (1) chemical technology to modify the **adsorption** characteristics of particulate systems toward gases and liquids, (2) diagnostic tests and immunological assays, and (3) delivery of drugs modifying uptake by the MPS. In this chapter we will focus on drug delivery systems that modify the normal uptake of particulates by the MPS. The benefits of anti-aging research have evolved in the last decade because of the significant relationship between the aging process and age-related diseases (Fernandes 2016). Therefore, the potential of surface-modified particulate systems has immense potential in age-related diseases, like cardiovascular diseases, cancer, and neuro-degenerative diseases (Magalhães et al. 2017).

14.2 Rationale of Using Particulate System and Concept of Biorecognition

There are several factors that should be considered to study the uptake of particulate systems by the mononuclear phagocyte system.

14.2.1 The Mononuclear Phagocyte System

Macrophages, commonly defined as mononuclear phagocytes (previously known as the reticuloendothelial system), were the first cell type identified as protecting the host from antigenic invasion. During the last 100 plus years since Metchnikoff (1891) discovered macrophages, they have been identified as the major mediators of humoral and cell-mediated immunity. Macrophages develop from a myelomonocytic **stem cell** in the bone marrow through monoblast, promonocyte, and monocyte stages until they form structurally heterogeneous tissue macrophages. In their early lifecycle the macrophages exist briefly in the bloodstream as adolescent cells called monocytes and constitute 3–7% of peripheral blood leukocytes. On reaching the tissues, monocytes undergo transformation to tissue macrophages and they are named based on a residency of 2–3 months as (Roitt et al. 1996): circulating blood monocytes, Kupffer cells in liver, various macrophages and microglia in brain. Macrophages can be of a wide variety of shapes depending on their residency, normally measuring 10–40 μm in diameter. The cells contain vacuoles and an approximately ovoid nucleus of 6–12 μm in diameter. The perinuclear cytoplasm contains mitochondria, many lysosomes, endoplasmic reticulum, and a Golgi apparatus, therefore, can synthesize and secrete proteins. The membrane proteins of macrophages have a rapid turnover half-life of 7 h that varies with receptor engagement (Elgert 1996).

The predominant role of macrophages is to remove particulate antigens by **phagocytosis**. They recognize, remove, and respond to foreign bodies and macromolecular ligands (Gordon 1987) by virtue of their expression of a variety of plasma membrane receptors for opsonized targets and also by direct recognition by the so-called pattern recognition receptors (Moretti and Blander 2014; Medzhitov and Janeway 1997). Macrophages internalize particulate antigens either by phagocytosis or receptor-mediated endocytosis, and digest most of them by lysosomal proteolysis. Some of the antigens are re-expressed as a fragment on the macrophage surface in relation to class II **major histocompatibility complex** (MHC) molecules that are presented to the **T cells**. Macrophages carry many proteins on their surfaces, some of which are receptors for antibodies or complements. Clearance of particles from the bloodstream is greatly enhanced if specific antibodies are present on the surface. Complexes between positively and negatively charged components (Law and Levine 1977) and opsonization increases the trapping efficiency of neutrophils and macrophages. It is possible to blockade the mononuclear phagocyte system by injecting a very large dose of colloidal carbon intravenously. Thereupon, the animal might be infected with any type of pathogenic microorganism.

14.2.2 Adsorption of Proteins to Surfaces

Proteins are complex biological molecules that contain a range of components that may all or partially interact with surfaces. Because of the surface-active properties of proteins, they tend to aggregate at interfaces and readily adsorb, especially if the surface is hydrophobic (Kawaguchi 1985). The cell interactions are mediated through layers of adsorbed proteins (Lai 2018). Andrade (1987) presented a summary of the hypothesis (Table 14.1) related to protein adsorption on the surfaces, the predominant factors being surface charge, surface energy, interfacial free energy, and surface motion (Sawyer 1984; Andrade 1976; Neumann 1979; Chin et al. 1978; Andrade and Halady 1986; Leininger 1972; Kim 1974; Nyilas and Ward 1977). The fate of a particulate system in contact with blood depends on the composition and conformation of the protein that covers the surface of the particles. The interaction of the protein with the surface of the particles depends on the concentration as well as the size of the protein and leads to adsorption of the protein on the surface of the particulates (Vroman 1982; Wojcieowski and Brash 1993). Protein adsorption on any surface depends on the nature of the surface, whether it is hydrophilic or hydrophobic, and follows a sequence of events involving interaction of proteins, reversible attachment followed by conformational change of the surface and ending in a quasi-irreversible fixation (Lundstrom and Elwing 1990; Soderquist and Walton 1980). Van Oss et al. (1975) and Neumann et al. (1979) demonstrated that phagocytic engulfment occurred more readily as the material became more hydrophobic, while platelets adhered more readily to hydrophilic than hydrophobic surfaces. Random coil proteins such as caseins adsorb in thick layers (10–15.5 nm) while compact globular proteins like β-lactoglobulin produce much thinner layers. Due to the highly

Table 14.1 Classical hypotheses of surfaces and blood compatibility

Property	Biological response	References
Negative surface charge	Plasma protein and cell repulsion	Sawyer (1984)
Interfacial free energy (IFE)	Decrease in IFE decreases protein adsorption	Andrade (1976)
	Difference between interfacial tension of adsorbate and cell, and adsorbate and vapor, determines protein adsorption	Neumann (1979)
	High interfacial free energy provides heat of adsorption that drives conformational change and contact activation	Chin et al. (1978)
Surface energy	Decreased surface energy provides optimum compatibility with blood	Andrade and Halady (1986)
Adsorption	Albumin adsorption or immobilization results in decreased thrombosis	Leininger (1972)
	Surface-adsorbed glycoproteins especially fibrinogen results in platelet adhesion	Kim (1974)
Surface motion	Increased motion leads to decreased adsorption and denaturation	Nyilas and (Ward 1977)

folded structure, globular proteins can potentially undergo extensive conformational changes when adsorbed to surfaces while the random coil protein lies close to the surface, with part of the polypeptide chains extending in the aqueous phase (Mackie et al. 1991). The more stable globular proteins such as lysozyme and ribonuclease retain most of their native structure when adsorbed onto surface and are expected to desorb more readily on dilution, while the proteins such as IgG, serum albumin, and hemoglobin appear to lose most of their secondary structures (Haynes and Norde 1995). The actual thickness of the adsorbed layer is dependent on a number of factors, including pH, surface charge on the particles, charge on the protein, and extent of denaturation of the proteins. Moreover, the electrostatic interaction (at a specific pH) among the surface, the protein and the adjacent adsorbed protein molecules is important to determine stable adsorption. Van Oss et al. also presented a correlation between the contact angle on the surface of the bacteria and the average number of bacteria phagocytosed per neutrophil. Experimentation with liposomes show that accumulation of liposomes at the MPS is related to the interaction of liposomes with plasma proteins which is dependent on the phospholipid type (Allen 1991), surface charge and size (Monkkonen 1994), and membrane rigidity (Patel et al. 1983) that result in different nature of liposome clearance from the circulation (Senior 1987).

14.2.3 Phagocytosis (Opsonization) as a Surface Phenomenon

Proteins in the serum that adsorb on the surface of foreign materials are called opsonin—means a relish or a sauce in Greek, and thereby prepare the material to be recognized by the MPS as foreign bodies and are to be phagocytosed. Thus, opsonization is a process that prepares the surface of a material for phago cytosis by adsorbing certain compounds (Lai and Rogach 2017a, b). Van Oss et al. (1975) in their extensive treatise showed that addition of complement and antiserum to non-phagocytosed bacteria resulted in significant increase of contact angle, and the same concept could be applied to particulate systems. Normally, hydrophobic nanoparticles adsorb more proteins than the hydrophilic nanoparticles leading to higher opsonization and shorter blood circulation compared to hydrophilic nanoparticles (Nguyen 2017).

Normally, intravenous administration of most non-modified particulate systems leads to rapid uptake in the liver and spleen within 5–10 min as has been reported with cyanoacrylate (Gipps 1988), polystyrene (Illum et al. 1986), polyacryl starch (Laakso et al. 1986), polyhydroxybutyrate (Koosha 1989), and albumin particles (Sugibayashi 1977). To localize the drugs in tissues or even to keep the particulates circulating in blood for longer periods of time is a challenge. The adsorption of proteins (opsonization) dictates the organ distribution of particulate systems, while not only the amount and type of the protein but also the protein conformation can determine the in vivo distribution (Patel and Moghimi 1990). Recently, Cao et al. demonstrated that protein binding affinity (equilibrium association constant) of polymeric nanoparticles can be correlated with in vivo fate of nanoparticles (Cao 2020). Therefore, if targeting is desired in the liver and spleen tissues, we would want quick opsonization and if we want the opposite, i.e., longer circulation time in the blood, we would like to have delayed or minimized opsonization.

14.2.4 Biopharmaceutical Factors Affecting the Uptake of Particulate Systems

There are three basic physical factors that affect the surface properties of the particulate systems leading to promotion of phagocytosis; hydrophobicity of the surface, surface charge, and the size of the particulate system. The major problem of the current carriers used in particulate drug delivery that includes biodegradable and non-biodegradable polymers and lipids is their hydrophobic nature. The hydrophobicity of the surface determines the interaction of the particulate systems with blood leading to opsonization and successive removal by phagocytosis. In case of non-biodegradable polymers, the contact angle may be close to 90°, while in case of biodegradable polymers the contact angle may be around 60–75°, which could be related to their chemical structures. It has been mentioned earlier that hydrophobic particles get opsonized quickly. Increase in surface hydrophobicity leads to enhanced adherence

and ingestion by phagocytes. Surface-modified hydrophilic albumin microparticles showed a reduced uptake in cultures of mouse peritoneal macrophages compared to hydrophobic non-modified particles (Artursson et al. 1983). The particles rapidly phagocytosed in the cell culture mimicking fast clearance from the circulation in vivo. Although a relationship between the reduction in surface hydrophobicity of coating films and the uptake by MPS using contact angle measurement has been described, prediction of hydrophobicity using contact angle measurement may not be the best technique, and the details are described later under the methods to determine hydrophobicity.

For intravenous delivery of particulate systems, it is not desirable to have any particles above 5 μm that could clog the vessels. The concept of filtration of drugs by the lung macrophages was exploited to deliver drugs to lungs using albumin microspheres (Illum and Davis 1982). Normally, the particles that bypass the lung capillary are taken up by the macrophages in the liver or the spleen. Zilversmit et al. documented the effect of size of gold particles on the rate of clearance from the blood compartment (Zilversmit et al. 1952). Macrophages phagocytose large vesicles more rapidly than the small vesicles. The size dependency of liposomes on organ distribution demonstrated (Diederichs 1996) small unilameller systems being less rapidly cleared from the system than the large multilamellar vesicles (Devine 1994). In vivo studies on the clearance of colloidal particles from the circulation and their uptake by liver macrophages have demonstrated the particle size effects (Yokoyama 1975; Scott et al. 1967; Juliano and Stemp 1975). In fact, it has been shown that reduction of the particle size alone could improve cellular uptake, irrespective of the other surface properties of nanoparticles (Cho 2010). While clathrin-mediated endocytosis is the predominant mechanism for less than 200 nm particles, caveolae-mediated processes occur up to about 500 nm (Rejman 2004). A number of studies showed that around 50 nm is the optimum size range for cellular uptake in the in vitro experiments (Elias 2013; Jiang 2008; Lu 2009). Recent studies revealed that phagocytosis by macrophages depends on the particle shape (Champion and Mitragotri 2006). Particles with aspect ratio of about three were internalized four times faster than spherical particles of the same volume. In addition, it was also shown the interplay of size and shape in the process of phagocytosis (Champion and Mitragotri 2009).

Particulate colloidal systems could possess anionic or cationic charge, or they could be neutral. The electrostatic stabilization of particulate colloids in dispersion is essential to avoid particle growth causing embolism. Normally, the anionic particles are eliminated faster from blood than positively charged or neutral ones (Petrak 1993; Tabata and Ikada 1988). However, the exclusive effect of surface charge of particles and their clearance from the blood compartment are very difficult to estimate and thus literature reports contradictory results. Van Oss (1978) stated that the zeta potential does not appear to be directly linked to the facility with which cells become phagocytosed, and that the connection between phagocytosis and zeta potential (if any) is far from simple. In contrast, Stossel et al. (1972) concluded that particles with large surface charge (negative or positive) are cleared rapidly by macrophages in vitro, while systems with low surface charge are cleared slowly. In

most instances, the surface charge is intimately related to surface hydrophobicity and size. According to Van Oss, colloidal particles presenting hydrophilic surfaces with a low contact angle will be almost ignored by phagocytic systems. No difference in blood circulation times and organ accumulation between different nanoparticle preparations with positive, neutral, and negative surface charges was 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 (Roser et al. 1998). Within 30 min after injection into a rat, anionic Aco-HSA liposomes (human serum albumin derivatized with cis-aconitic anhydride covalently coupled to liposomes with a size of approximately 100 nm) were completely cleared from the blood and almost exclusively taken up by the liver, whereas in control liposomes 80% was present in the blood at the time point. Endothelial cells were shown to account for almost two-thirds of the hepatic uptake of the Aco-HSA liposomes, the remainder being recovered mainly in the liver macrophages (Kupffer cells) (Kamps 1994). The surface charge affects the particle–cell interaction at short distances. Involvement of immunoglobulin in the particle–cell interaction (as in receptor mediated endocytosis) reduces the effect of surface charge (Schwendner et al. 1984), indicating that the effect of surface charge of colloids is negligible in receptor-mediated phagocytosis of the particles. Roerdink et al. concluded that opsonization of liposomes with complement greatly stimulates uptake of liposomes by murine macrophages. However, most of the opsonization conferred by complement can be prevented by the presence of negatively charged membrane lipids (Roerdink 1983).

14.3 Surface Modification or Steric Protection with Polymers

In order to protect particulate systems from being engulfed by the phagocytes, normally they are attached to, or coated with a protective polymer. There are two major methods to protect the particulate systems: (1) by grafting a polymer chain covalently on to the surface of a particle, and (2) by adsorption or incorporation of protective polymers on the surface of the particulate systems. In both situations, the hydrophilic parts protrude toward the bulk solution and protect the particles from interaction with the blood proteins (Blunk 1993). The term “steric stabilization” was introduced by Naper in 1983 (Naper 1983). The major work in this area has been done with liposomes. One of the most popular methods is to coat liposomes with some hydrophilic protective polymer, like polyethylene glycol (PEG) (Kilbanov 1990). Coating of the liposomes with PEG sterically hinders the interaction of the blood components with the liposome surface (Allen 1994; Woodle 1993), thereby preventing opsonization of the liposome surface and the engulfment of the liposomes by the MPS (Senior 1987). Steric stabilization occurs as a result of repulsion between two overlapping polymer layers (Klein 1986). There are basically three parameters that should be fulfilled for the criteria of steric repulsion (Amiji et al. 1994):

1. Surface-modifying polymer should be tightly bound to the surface and not replaced by plasma components.
2. A portion of the polymer should extend in the bulk aqueous medium, with optimal extensions and flexibility of the polymer segments that determines the dominance of steric repulsion over the **van der Waals attractive forces**. Therefore, block copolymers with hydrophilic and hydrophobic chains are more effective than homopolymers (Naper 1983).
3. The surface-modifying polymer should coat the surface completely; any incomplete coverage of the surface may leave it prone to opsonization.

The bypassing of MPS by particulate systems mainly depends on the polymer structure and characteristics and determines the kinetics of disposition of the polymers in the body. Factors that affect the disposition of intravascularly administered polymers are the polymer size and interaction with the blood components. Normally, large polymers are subject to more opsonization depending on the interactive moieties s on the polymer chains and the opsonins available in the immunocomplex (Ehlenberger and Nussenzweig 1977), rendering the large polymers more prone to phagocytosis. Ross et al. showed that it was not a single opsonin interaction but multiple opsonin interactions with polymers being involved in the process (Ross et al. 1985). Immunocomplex half-lives depend on the opsonin molecules attached to it and could vary depending on whether they are immediately phagocytosed (Brown et al. 1970) and if not, they could even circulate in the body for a few days (Atkinson and Frank 1974). In case of small polymers, opsonization followed by phagocytosis is rather less plausible than the more obvious renal clearance (Delgado et al. 1992).

A varied number of functional groups may be responsible for surface recognition. A number of receptors can recognize carbohydrates, especially receptors in the liver (Rice and Lee 1990). Various receptors can bind to peptide side chains. In fact, most of the functional groups interact with the immunocomplexes, to a varied extent, and the polymers with several positively charged groups or highly hydrophobic groups interact, especially in vivo. Hydrophilic polymers with low nucleophilicity appear to have the best circulating properties. **Amphiphilic polymers** used for surface modification consist of a hydrophobic part that adsorbs on the particle surface and a hydrophilic part that protrudes in the solution and protects the particles from interactions with blood components. Torchilin et al. reported that the surface-grafted chains of flexible and hydrophilic polymers form dense "conformational clouds" preventing other macromolecules from interaction with the surface, both in the form of dense particle coating as well as in the form of a relatively loose brush (Torchilin and Trubetskoy 1995). Jeon et al. studied the interactions of surface-modifying polymers with blood proteins and established relationships between steric repulsion, van der Waals attraction and hydrophobic attraction, and the surface density and chain length of polyethylene oxide (PEO). High surface density and long chain length of PEO are desirable for protein resistance. Also, the surface density has a greater effect than chain length on steric repulsion (Jeon 1991). The biodistribution of surface-modified particles is dependent on the competing processes of reduction in the adsorption of opsonins and the selective adsorption of certain plasma proteins

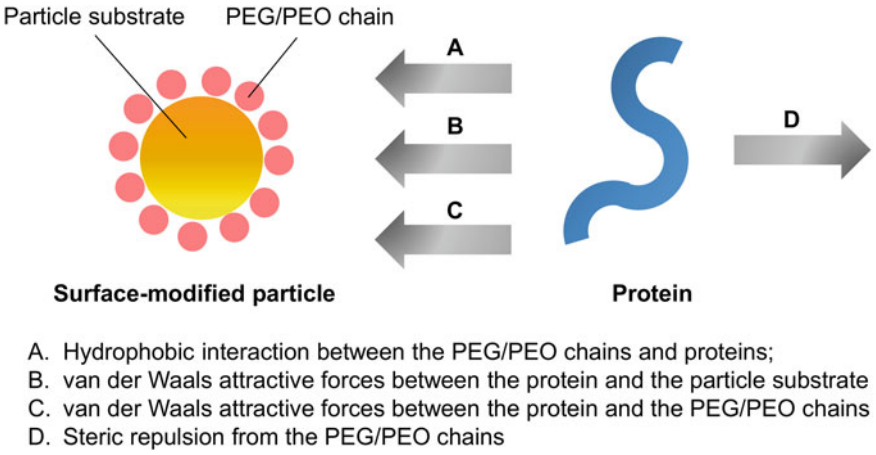

Fig. 14.1 Interactions between a surface-modified particle and the opsonins

(dysopsonins) (Moghimi 1993). As the PEO chains are compressed in solution, the surface density of PEO increases gradually. This might make the coated surface hydrophobic,therefore, an optimum chain length of coating polymers is necessary to impart hydrophilic properties (Jeon and Andrade 1991). Another interesting aspect is that hydrophilicity is not enough to protect the particles. Dextran-coated liposomes were cleared faster from the circulation than PEG-coated liposomes, although dextran is more hydrophilic than PEG (Pain 1984). Also, the chain flexibility that contributes to providing the long-circulating feature could have a varied number of chain conformations (Torchilin and Papisov 1994; Blume and Cevc 1993). Figure 14.1 illustrates the interactions of a surface-modified particle and the blood proteins.

14.3.1 Polyethylene Glycol (PEG)

Minimization of polymer interactions with biological systems is the prime requirement in the design of long-circulating particulates. Major groundbreaking work was initiated with the reporting of surface-modified long-circulating liposomes such as “stealth liposomes” (Allen 1989) or sterically stabilized liposomes (Papahdjopoulos 1991). The effect of PEG in surface modification to decrease the phagocytosis of particulates has been widely studied in liposomes (Senior 1991; Filion and Philips 1997) and polymeric particles (Allemann 1995). An advantage of using PEG in surface modification is that it is non-toxic and is approved by the FDA for internal use (Harris 1985). In recent years, amphiphilic molecules containing both hydrophobic and hydrophilic parts have been employed to modify the surface of particulate systems. The longer action of liposomal incorporated ganglioside (GM1) was achieved with a coating of PEG (Allen and Chonn 1987; Mori 1991). The

phenomenon is explained by involvement of surface charge and the hydrophilicity of PEG-coated liposomes (Gabizon and Papahadjopoulos 1992) and reduced opsonization of plasma proteins on the surface of particulates (Lasic 1991). The easiest method to coat particle surfaces is to adsorb amphiphilic polymers like PEG, provided the surface is hydrophobic. These polymers undergo hydrophobic interactions with the particulate surface, while their hydrophilic parts get exposed to the plasma proteins on intravenous administration (Blunk 1993). However, there are limited literature reports on the surface modification of nanoparticles using adsorption or incorporation of PEG within the polymer matrix. The other way to protect the surface is to graft a polymer chain onto the surface by covalent bonding to induce "steric stabilization" (Naper 1983).

In the adsorption method, the matrix polymer and PEG or substituted PEG is dissolved in a common solvent like dichloromethane and the particles are formed by W/O/W solvent evaporation method or spray drying process. It was demonstrated that PEG was homogeneously dispersed on the microspheres and decreased phagocytosis to a significant extent (Lacasse 1988). X-ray photoelectron spectroscopy confirmed that the greater the amount of PEG-distearate in the formulation, the higher is its concentration on the surface (Lacasse et al. 1998). Also, a range of polylactide-PEG block copolymers either self-disperse in aqueous medium to form micelles or produce stable particles, where the drug is entrapped in the hydrophobic matrix of polylactide coated with hydrophilic PEG or its derivative. A number of studies have been conducted with polystyrene nanoparticles with surface-adsorbed PEG and blocks of poly(propylene glycol), and it was reported that the adsorption was kinetically controlled and decreased with an increase in surface roughness and polarity (Illum and Davis 1983). High molecular weight PEG has been shown to reduce surface roughness of the polymer particles which could be due to reduction of surface tension between the particles and aqueous phase (Monnier 2016). Although non-biodegradable polystyrene particles are not a realistic therapeutic system, this model was later applied to PLGA microparticles coated by amphiphilic diblock PEG-PLA copolymers (Dunn 1994). The major problem with adsorbed polymers is that they might efficiently desorb in vivo, especially in the presence of blood components with high affinity for the particle surface (Petrak 1993).

It has now been well documented that PEG covalently bonded to proteins forms macromolecular conjugates with longer blood circulation time than native proteins, with less immunogenic reactions (Abuchowski 1977). A review thoroughly covers the details of PEGylation reactions and biochemical and biological characterization (Bailon and Berthold 1998). On attaching the PEG or PEG derivatives, it has been reported that the **graft polymer** of PEG on to poly(lactide-co-glycolide) or poly(D,L-lactide) can be synthesized by ring opening polymerization of the respective polymer in the presence of a catalyst, stannous octoate (Churchill and Hutchinson 1986; Deng 1990). This catalyst is very effective and widely used to synthesize PLA-PEG copolymers (Kricheldorf and Meier-Haack 1993) and is approved by FDA for use as a food stabilizer (Gilding and Reed 1979). In case of liposomes, the PEG-grafted polymers appear to be better than using other polymers for grafting due to better stability of the coating, and increased blood residence time (Allen 1994). Also, the blood half-life

of PEG increases from 18 min to 1 day as the molecular weight increases from 6,000 to 190,000 (Yamaoka et al. 1994). An important factor that should be kept in mind while formulating particulates with PEG is that PEG given intravenously in large doses over a prolonged period of time may cause nephrotoxicity (Erickson 1996). Although a large therapeutic window (approximately 600-fold) exists between the maximum PEG burden from a currently marketed biological agent and the doses of PEG associated with human toxicity, molecular weight of PEG is known to have significant effect acute toxicity (LD_{50}) in rats and mouse (Webster et al. 2009). It has also been shown that pegylation of particulate systems could cause generation of anti-PEG-IgM (Wang et al. 2007; Ishida 2007). Densities and chain-length of PEG on the surface of particles often cause steric shielding (Hatakeyama et al. 2013; Fang 2017), thereby preventing their interaction with cellular receptors (Wang and Thanou 2010; Pelaz 2015; Schöttler et al. 2016; Barui 2020). Therefore, very careful optimization of PEG orientation on the surface of nanoparticles is desirable to effect maximum cellular uptake of particles. A list of more representative examples demonstrating the use of PEG in surface modification of polymer nanoparticles has been shown in Table 14.2 (Lacasse et al. 1998; Hagan 1995; Gref 1994; Stolnik 1994; Dunn 1994; Peracchia 1994; Verrecchia 1995; Yeh 1995; Piskin 1995; Li 2000; Pean 1999; Lacasse 1998; Hawley et al. 1997). They illustrate the versatility and wide use of PEG in the design and development of polymeric nanoparticle systems in drug delivery.

14.3.2 Block Copolymers of Ethylene Oxide and/or Propylene Oxide

The amphiphilic surface modifiers, polyethylene oxide (PEO)/polypropylene oxide (PPO), have been most successful in extending the circulation half-life of particulate systems (Abuchowski 1977). Particulate carriers are either grafted to PEO (Harper 1991; Maste 1994) or adsorb amphiphilic PEO copolymers (Moghimi 1993). A number of amphiphilic PEO and PPO copolymers of different compositions and molecular weights are available as poloxamers and poloxamines. Poloxamers are ABA block copolymers represented as EO–PO–EO, while poloxamines consist of four PEO and PPO blocks joined together by an ethylene diamine bridge represented as $[EO–PO]_2–N–CH_2–CH_2–N–[PO–EO]_2$. Poloxamers and poloxamines are marketed by BASF Performance Chemicals, NJ, under the trade names of Pluronic® and Tetronic®, respectively. In addition, BASF also markets Pluronic® R as PO-EO-PO and Tetronic® R as $[PO\text{-}EO]_2–N–CH_2–CH_2–N–[EO–PO]_2$. Reversing the hydrophobic and hydrophilic blocks creates surfactants similar to Pluronic surfactants, but with some important differences. While the Pluronic surfactants are better emulsifiers and dispersants and cover a broader range of molecular weights, Pluronic® R surfactants have lower foaming, greater defoaming, and reduced gelling tendencies. In addition, Pluronic® R surfactants are terminated by secondary hydroxyl groups, which have lower reactivity and acidity than the primary hydroxyl

Table 14.2 Polyethylene glycol-modified polymer particulates

Objective	Surface-modifying polymer	Particulate matrix polymer	Method of preparation	Active ingredient	References
Study of surface morphology of spray-dried particulate	PEG 400 distearate	Poly(D,L-lactic acid)	Blend of polymers in DCM and spray drying	–	Hagan (1995)
PLA-PEG micelles	PEG	Poly(D,L-lactic acid) (PLA)	Graft copolymer of PLA-PEG in ratio of 1.5:2 and 2:5	Testosterone	Gref (1994)
PLGA grafted with PEG	PEG	Poly(lactide-co-glycolide)	Graft copolymer of PLGA and PEG	Lidocaine	Stolnik (1994)
PLA-PEG adsorbed onto the surface of PLGA nanospheres	PLA-methoxy-PEG	Poly(lactide-co-glycolide)	PLA-PEG adsorbed after preparation of PLGA nanospheres by precipitation solvent evaporation	–	Dunn (1994)
In vivo biodistribution	PLA-PEG	Poly(lactide-co-glycolide)	PLA-PEG adsorbed after preparation of PLGA nanospheres	–	Peracchia (1994)
Physicochemical characterization	PEG	Polyesters and polyanhydrides	Emulsification solvent evaporation—grafted PEG	Lidocaine, prednisolone	Verrecchia (1995)
Comparison of surface and non-surface modified particles	Methoxy-PEG	Poly(D,L-lactide)	Solvent diffusion of PLA-methoxy-PEG solution	Albumin	Yeh (1995)
Delivery of proteins using PLGA microparticles	PEG	PLGA	Blend of PLGA and PEG using multiple emulsion solvent evaporation method	Ovalbumin	Piskin (1995)
PLA-PEG micelles	PEG	PLA	Copolymer made by transesterification	–	Li (2000)

(continued)

Table 14.2 (continued)

Objective	Surface-modifying polymer	Particulate matrix polymer	Method of preparation	Active ingredient	References
Protein stability	PEG	PLA	PLA-PEG bulk ring opening polymerization—emulsion solvent evaporation	Glucose oxidase	Pean (1999)
Protein stability on co-encapsulation	PEG 400	PLGA	Blend of PEG and PLGA	Nerve growth factor	Lacasse (1998)
Effect of plasma protein adsorption and phagocytosis	PEG	PLGA, PLA and polyanhydride	Blend of methoxy PEG with PLGA, PLA and polyanhydride	–	Hawley et al. (1997)
Comparison of PEG coated nanoparticles on lymph node uptake	PEG	PLGA and PEG-PLGA-PLA	Coating by adsorption and coprecipitation—separation of unadsorbed polymer	^{125}Iodine and ^{111}Indium oxine	Abuchowski (1977)

groups terminating Pluronic® surfactants and the same applies for Tetronic® R and Tetronic® (Performance Chemicals and Pluronic and Tetronic Surfactants 2020). Only a few members among the poloxamer and poloxamine series are able to modify the surface characteristics of the particulate systems. Normally, poloxamers with high molecular weights such as 338 provide an effective steric barrier (Illum and Davis 1984), whereas poloxamers with lower molecular weight such as 235 do not (Illum 1987). In recent years, the most promising copolymers used for surface modification of particulate systems appear to be PEO grafted to a biodegradable polymer, such as poly(D,L-Lactide)-PEO (Stevels 1995) and poly(caprolactone)-PEO (Peracchia 1994), by ring-opening polymerization in the presence of methoxy-PEO and stannous octoate as the catalyst. It is postulated that, in contact with water, highly hydrated and flexible PEO forms dense "conformational clouds" over the particulate surface, inhibiting the interaction with opsonins and the phagocytic cells (Torchilin and Papisov 1994). The adsorption of PEO-based surfactants as well as PLA-PEO block copolymers on PLGA or PLA proceeds via hydrophobic interactions between the hydrophobic particle surface and the hydrophobic moieties, while the hydrophilic PEO parts form a "hair-like" coat around the particle. However, due to the partial reversible nature of the adsorption process, it is difficult to predict the stability of the adsorbed steric barrier. In order to solve this problem, PEO-grafted nanoparticles have been developed by direct grafting of PEO moieties on the preformed particles (Muller and Kissel 1993) or by in situ polymerization in the presence of PEO moieties (Peracchia 1997).

Most of the earlier studies on surface modification with poloxamers reported the coating of non-biodegradable particles of poly(methyl methacrylate) or polystyrene. PEO adsorbed surfaces have been reported using PEO homopolymers of high molecular weight that adsorb effectively (Kato 1981). It has been reported that 30 PO residue Pluronics adsorbed on hydrophobic surfaces did not decrease adsorption of albumin significantly while 56 PO residues of Pluronics were effective in the prevention of protein adsorption (Amiji and Park 1992). Labeled polystyrene microparticles of specific size range were incubated with poloxamer 338 for 24 h, and disposition was recorded in experimental animals after intravenous administration. It was reported that poloxamer 338 and poloxamine 908 were effective in reducing the liver uptake of the labeled poly(methyl methacrylate) nanoparticles, while the uptake of nanoparticles in non-MPS organs like heart, GI-tract, ovary, muscles, and brain were significantly increased (Troster et al. 1990). Alyautdin et al. demonstrated that the polysorbate 80 coating of analgesic dalargin adsorbed poly(butyl cyanoacrylate) nanoparticles delivers the drug across the blood–brain barrier compared to dalargin solution, dalargin bound to nanoparticles without coating with polysorbate 80, and a simple mixture of dalargin, nanoparticle, and polysorbate 80 mixed directly before IV injection (Alyautdin 1995). It was reported by Muller et al. that ethoxylated polymers and surfactants can be easily adsorbed onto polystyrene particle surfaces,however, it was difficult to coat the polyester (polylactide, polylactide/glycolide nanoparticle surface with the same ethoxylated polymers (Muller and Wallis 1993). This is possibly due to the inherent hydrophilic surface of polyester particles produced by W/O/W solvent evaporation in aqueous polyvinyl alcohol solution. Solid lipid

nanoparticles (SLN) produced by dispersing melted lipids in an aqueous solution of poloxamine 908 or poloxamer 407 proved more efficient in avoiding phagocytic uptake than polystyrene particles surface modified with the same polymers (Muller 1996). Considering the fact that SLNs are tenfold less toxic than the polylactide nanoparticles (Maaben 1993) and 100-fold less toxic than the cyanoacrylate particles (Lherm 1992), they are one of the most viable carrier systems for long circulation of drugs. Blending of Pluronic® copolymers with PLG or PLGA is a logical approach toward the development of the W/O/O microencapsulation technique. Yeh et al. studied the physicochemical characteristics of PLG blended with hydrophilic Pluronic® F127 and more hydrophobic Pluronic® L121 (Yeh et al. 1996). Secondary ion-mass spectroscopy indicated the presence of PEO-PPO on the surface of PLG microspheres produced by W/O/W solvent evaporation in the solution of PEO-PPO surfactants (Coombes 1994).

Thus, biodegradable triblock copolymers are potential carrier systems for surface modification of particulate systems. Moreover, if a protein drug is encapsulated in the particles, its stability is protected as the higher hydrophilicity of PEO block that leads to a higher water content in the matrix, possibly preventing aggregation of proteins (Kissel 1994). ABA triblock copolymers, consisting of poly(L-Lactic acid) or poly(L-Lactic-co-glycolic acid) and poly(ethylene oxide) were synthesized by bulk polymerization, using aluminum tri-isopropoxide as catalyst (Youxin and Kissel 1993). Normally nanoparticles are prepared by emulsion solvent evaporation of PLA-PEO block copolymer, in which PLA is racemic (M = 30,000) and linked to PEO (M = 2,000). After solubilizing it in acetone (25–50 g/L) the polymers are precipitated in pure water (Labarre 1994). In a study, Gurny et al. reported various blends of fluorescent-labeled PLA and PLA-PEO diblock copolymers, produced by a salting out process (Leroux 1995), and a clear relationship between the PEO contents, and a decrease in the in vitro cell uptake was demonstrated (Jaeghere 1999). An interesting process for synthesis of triblock poly(L-Lactide)-block-poly(oxyethylene)-block-poly(L-Lactide) copolymer in the absence of any added catalyst has been suggested. This method may be advantageous as it does not leave any trace of non-biodegradable catalysts, but it is not competitive against the catalyzed methods since very long reaction times (few days) are necessary to have 70–90% yield (Cerrai and Tricoli 1993). Ronneberger et al. (1997) studied the biocompatibility of microparticles made from ABA triblock copolymers and observed that implanted microparticles caused an initial acute but localized inflammatory response. Muscle tissue surrounding the injection sites did not show irreversible changes such as necrosis and degeneration. The implantation sites were gradually replaced by collagenous tissue during the course of degradation. The results show that the microparticles prepared from ABA-triblock copolymers can be considered as a biocompatible carrier system with properties similar to PLGA or PLA.

14.4 Surface-Modified Particulates in Sequestering Multidrug Resistance Proteins

Success in the treatment of some disseminated cancers with chemotherapy has led to understand why many other cancers are naturally resistant to anti-cancer drugs or become resistant to chemotherapy after several rounds of treatment. Although over 50 anti-neoplastic small-molecule drugs are in use, only a few are effective for a specific tumor type because of intrinsic or primary drug resistance. The initial and subsequent chemotherapy treatments allow a tumor to develop acquired or secondary resistance because malignant cells that survive the drug are resistant to that drug. The broad-spectrum resistance to structurally and mechanistically diverse anti-cancer agents constitutes the multidrug resistance (MDR) phenotype. Multidrug resistance of cancer cells is a serious challenge in the treatment of neoplastic diseases and is the leading cause of the failure of chemotherapy. Cancer cell chemoresistance is based on the development of several mechanisms among which one of the most important concerns is the overexpression of membrane proteins that remove cytotoxic compounds from the cytoplasm as an **efflux pump**. The leading archetype of these proteins is the P-glycoprotein, a member of the ATP-binding cassette (ABC) superfamily of transporters, or traffic ATPases. Tumor cells carrying this phenotype are characterized by the overexpression of an energy-dependent drug transport protein, P-glycoprotein (P-gp) (Ling 1987; Ban 1992), belonging to the superfamily of the ATP-binding cassette (ABC) (Ling 1997; Krishnan et al. 1997). The overexpression results in a decreased accumulation of the drug within the cancer cell because the cell can efficiently pump out the hydrophobic anti-cancer drug molecules (Ford and Hait 1990; Gottesman and Pastan 1993). It has been shown that a major mechanism of resistance of cancer cells to natural product anti-cancer drugs such as adriamycin, etoposide, vinblastine, actinomycin D, and taxol is expression P-glycoprotein (P-gp) or the multidrug transporter (Gottesman 1995). This pump system contributes to drug resistance in about 50% of human cancers by preventing adequate exposure of anti-cancer drugs in cancer cells.

In the recent years, a number of other drug efflux transport proteins, 190–210 kDa multidrug resistance associated protein (MRP) (Barrand et al. 1997; Hollo 1996), 110 kDa lung resistance associated protein (LRP) (Izquierdo 1996), and new genes, have been discovered in cancer cells with a multiple drug resistance phenotype (Baggetto 1997). While P-gp is thought to have a major role in acquired drug resistance (Abe 1996), the widespread expression of MRP in many solid organ and untreated tumor cells (Kruh 1995) suggests MRP may have a more important role in intrinsic drug resistance. Like P-gp, MRP is also an ATP-dependent efflux pump that actively transports selected chemotherapeutic agents. MRP has different substrate characteristics and different inhibitor specificity from P-gp and has a broad specificity for amphiphilic anions (Jedlitschky 1996). The ABC transporter breast cancer resistance protein (BCRP) has been cloned, sequenced and developed into a diagnostic tool (Ross 2000; Natarajan et al. 2015).

In order to decrease the toxicity, to improve bioavailability to target tissue and to enhance the selectivity of existing drugs, many drug-delivery systems for chemotherapeutic agents have been proposed in recent years (Gupta 1990). Biodegradable nanoparticles and lipid nanoemulsions have received a growing interest for drug targeting, because they can be easily prepared with well-defined biodegradable polymers (Allemann et al. 1993) and lipids. The reason of targeting tumors with nanoparticles is because certain neoplastic cells have been found to exhibit an enhanced endocytotic activity (Kreuter 1983) which could be due to cell surface expression of critical molecules (Elkin et al. 2015). In addition, since capillaries having an increased vascular permeability supply some particular tumors, one can anticipate that nanoparticles will gain access to extravascular tumoral cells (Jain 1987). Another interesting property of anti-cancer drug-loaded nanoparticles is their ability to overcome pleiotropic resistance. In vitro studies evaluating the efficacy of nanoparticulate delivery systems have been used to evaluate the efficacy of anti-neoplastic agents. In vitro studies evaluating the efficacy of nanoparticles on MDR cells have been demonstrated with doxorubicin (Tokes et al. 1982; Kubiak 1989; Nemati et al. 1994). By coupling doxorubicin to nanospheres, DXR efflux from the tumoral U-937 cells was considerably reduced (Astier et al. 1988). Two mechanisms have been proposed to explain how the nanoparticles counteract the MDR: (i) inability of P-glycoprotein to reject nanospheres-bound DXR outside the cell, (ii) DXR bound to nanospheres can efficiently interact with the membrane of the resistant cells, inducing at the final stage a perforation of the cytoplasmic membrane (Rogers et al. 1983) and is dependent on the nanospheres density (Astier et al. 1988). Although the reduction in the general toxicity of anti-cancer drugs bound to nanoparticles has been demonstrated in a number of cases (Couvreur et al. 1982), in certain situations anti-cancer drugs bound to nanoparticles have often been associated with a higher acute toxicity (Kreuter and Hartmann 1983). The increase of toxicity could be attributed to the accumulation of the carrier in the organs of the mononuclear phagocyte system, such as spleen (Brasseur et al. 1980). This confirms the importance of developing drug delivery systems that can avoid the MPS (when it is not the target site) and of designing nanoparticulate systems having appropriate physicochemical properties.

One of the major applications of long-circulating liposomes has been in cancer chemotherapy. Cytosine arabinoside, vincristine, epirubicin, and doxorubicin are among the drugs that have been developed (Gabizon 1994). The doxorubicin containing liposome based on Stealth® technology, Doxil® (Janssen) is commercially available for use in AIDS-related Kaposi's sarcoma. Because of the small particle size of 50 nm, Daunosome® (Gilead Sciences) is also considered a long-circulating formulation. In addition, Genexol-PM® (Samyang Biopharm), Naulasta® (Amgen), Oncaspar® (Takeda) are also long-circulation formulations based on polymeric platforms.

14.5 Surface Modification as a Strategy to Target Non-MPS Organs

Surface modification of particulate systems not only reduces the clearance of the particles by MPS, but it also improves the availability of the drug, as the particles can increase the disposition of drugs in organs that do not belong to the MPS. Borchard et al. (1994) observed an increased uptake of surfactant-coated poly(methyl methacrylate) nanoparticles by bovine brain microvessel endothelial cell monolayers in vitro. Using fluorescent polysorbate 80 coated fluorescence isothiocyanate dextran labeled poly(butyl cyanoacrylate) nanoparticles, Kreuter et al. (1995, 1997) showed that surface-modified particulates can be taken up by the endothelial cells lining the brain blood vessels and demonstrated transport of fluorescence into the Purkinje cells of the brain shortly after intravenous injection.

Besides endocytosis, the other possibility by which the above drugs exhibit increased brain uptake may be inactivation of the P-glycoprotein efflux pump that is present in the brain endothelial cells. In another interesting observation, poloxamer 338 and poloxamine 908, non-ionic surfactants that are widely used as surface-modifying agent to bypass MPS, were found to be ineffective in transporting drugs across the blood–brain barrier while polysorbate 80 was found to be effective (Troster et al. 1990). A recent review described delivery of small molecule drugs as well as macromolecules across blood-brain barrier using surface modified nanoparticles (Tosi et al. 2020).

14.6 Summary and Outlooks

Effective systemic delivery is vital for the development of biogerontological interventions (Lai 2020; Lai 2013). Over the years, different strategies have been reported for tackling aging. For instance, whole-body knockout of *Pla2r1* in a murine model of premature aging has been found to decrease the reduction in the bone content (Griveau 2018). In addition, by manipulating isoprenylcysteine methylation in a premature aging mouse model via whole-body reduction of the expression and activity of isoprenylcysteine carboxyl methyltransferase (ICMT), body weight of the mouse is increased, the grip strength is normalized, and bone fractures and death of the mouse are prevented (Ibrahim 2013). These advances in anti-aging medicine, however, fail to be practiced in reality, partly because of the failure of systemic delivery for whole-body genetic and pharmacological treatment. Such failure is partly attributed to the rapid removal of the therapeutic agent from the blood circulation before the arrival of that agent to tissues. To enhance the efficiency of systemic delivery, prolonging the blood circulation time is one of the prerequisites. In this chapter, we have presented advances in surface modification strategies for optimization and modification of particulate systems. Based on the promising potential as evidenced by the literature, we anticipate that surface-modified particulate systems

will continue with their enormous promise in the delivery of a number of drugs not only by virtue of bypassing the mononuclear phagocyte system, but also in the treatment of multidrug resistant cancers and drug delivery across the blood–brain barrier. By taking the criteria discussed in this chapter into consideration during the design of the nanocarrier, it is possible to develop delivery systems with prolonged circulation half-life, avoiding the phagocytic uptake by the mononuclear phagocyte system, thus releasing drugs for a prolonged period of time, with better therapeutic efficacy and reduced toxicity.

Important Notes

- The electrostatic interaction (at a specific pH) between the surface and the protein and between adjacent adsorbed protein molecules is important to determine stable adsorption.
- Protein adsorption on any surface depends on the nature of the surface, whether it is hydrophilic or hydrophobic, and follows a sequence of events involving interaction of proteins.
- There are three basic physical factors that affect the surface properties of the particulate systems leading to promotion of phagocytosis: hydrophobicity of the surface, surface charge, and the size of the particulate system.
- Stability of the dispersed particulate systems in blood could be improved by manipulation of hydrophilicity and surface charge.
- Surface-modified particulates could be beneficial for drug delivery across blood–brain barrier and also in multidrug-resistant malignant tumors.

Questions for Future Research

- **How to optimize hydrophilicity, surface properties, and particle size for maximum circulation time in the blood?** It has been widely understood that the blood retention time of a carrier can be manipulated by changing the hydrophilicity, size, and surface properties. However, currently manipulation of these factors during carrier optimization is by trial-and-error method. Methods to more rationally optimize the properties of a carrier are in dire need.
- **Which PEGs would be the most suitable and effective one for surface modification?** Over the years, many PEG derivatives have been proposed based on the immunological considerations; however, right now it is poorly understood how different derivatives affect the ultimate performance of a carrier. Solving this problem may increase our understanding of the mechanisms and structure–activity relationships involved in the PEGylation of nanocarriers.

- **What would be the optimum PEG or PEO coating that will not cause steric hinderance for particle uptake by the target cells?** PEG or PEO coating has been extensively used for surface modification of nanoparticulate systems; however, they may cause steric hindrance and may ultimately reduce the efficiency of cellular uptake, leading to a reduction in the performance of the carrier in drug delivery. Strategies to help optimize the structure, composition, and thickness of the coating can enhance the efficiency in structural modification using PEG and PEO.
- **What would be the best approach for targeting of particulate systems to cancer tissues using surface-modified particles and active targeting moieties?** Cancer is an age-associated disease. Over the years, different agents (ranging from folic acid to transferrin) have been adopted to modify the surface of carriers so as to render the delivery systems into tumor-targeting agents. Differences in the targeting efficiency mediated by different ligands, however, have not been seriously compared till now. Studies in this aspect may help identify the best approach for targeting of particulate systems to cancer tissues.

Glossary

Adsorption Adhesion of molecules from a gas, liquid, or dissolved solid to a surface.

Amphiphilic polymers Polymers possessing both hydrophilic and lipophilic properties.

Efflux pump A proteinaceous transporter localized in the cytoplasmic membrane cells.

Graft polymer A branched copolymer with one or more side chains of a homopolymer attached to the backbone of the main chain.

Liposomes Spherical vesicles having at least one lipid bilayer. Liposomes can be used as a vehicle for administration of bioactive agents.

Macrophages White blood cells that surround and kill microorganisms, remove dead cells, and stimulate the action of other immune system cells.

Major histocompatibility complex Proteins that are essential for adaptive immunity.

Phagocytosis The process by which a cell uses its plasma membrane to engulf a large particle, giving rise to an internal compartment called the phagosome.

Stem cell A cell that has the ability to develop into many different cell types, from muscle cells to brain cells.

T cells Lymphocyte immune cells that protect the body from pathogens and responsible for immunity against cancer cells.

van der Waals attractive forces Weak non-covalent, non-ionic forces between atoms or molecules.

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