14 Factors Affecting the Clearance and Biodistribution of Polymeric Nanoparticles

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Contents

Abstract

Nanoparticles are promising drug delivery for various therapeutic applications. Pharmacokinetics is important to study the in vivo fate of nanoparticles. Biodistribution and clearance are the important parameters of pharmacokinetics to be considered. Impact of various characteristics of polymeric nanoparticles affects biodistribution and clearance of nanoparticles. The chapter focuses on four important characteristics of polymeric nanoparticles affecting their biodistribution and clearance.

Keywords

Clearance · Biodistribution · Polymeric nanoparticles

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1 Introduction

Nanodelivery systems are a comparatively new but quickly emerging field in which nanoscale materials are used as diagnostic tools or to administer therapeutic medicines to precise targets in a controlled mode [30, 57, 82, 84]. Nanoparticles can be turned into intelligent devices, encapsulating medicinal and imaging chemicals while also having stealth properties, by manipulating their size, surface features, and composition [69]. They are intended to alter the biodistribution and pharmacokinetics of the drugs, allowing for a higher dose to be delivered to a targeted disease tissue, in order to improve the therapeutic efficacy and render reduced toxicity. Many different materials and shapes of nanoparticles have been

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produced for use in disease therapy, and many of them have shown to be effective [59, 61, 78]. Currently, there are a number of nanopharmaceutical products in the market [10, 19, 29, 31, 34, 42, 43]. When using nanoparticles, several factors must be considered: distribution efficiency, therapy effects, and clearance [53, 66, 90, 95]. Clinical uses for nanoparticles with great efficacy and good biosafety are on the horizon. Therapeutic effectiveness of nanoparticles is inextricably tied to pharmacological and toxicological characteristics. The most significant elements for establishing a high therapeutical index and related clinical performance are drug target residence, maximal tolerated dose, and selectivity [7, 40, 49]. Optimizing drug pharmacokinetic qualities to improve therapeutic effects and prevent adverse effects is an important feature of nanoparticle formulation design, which involves considering not just the characteristics of nanoparticles but also pharmacokinetic characteristics. The interaction between body systems and nanoparticles is responsible for all therapy outcomes.

The shape and polymer content in the core and periphery of polymeric nanoparticles characterize them. Drug is either adsorbed on the surface or encapsulated inside the core part of the polymeric nanoparticles. Delivery formulation governs the release of drug either to be controlled, sustained, or triggered release [3]. Furthermore, the surface of the polymeric nanoparticles can be attached with functional groups to obtain certain added characteristics such as prolonged systemic residence time, minimal non-specific distribution, and/or target specific cell or tissue, for example, coating the surface of the nanoparticles with polyethylene glycol to prolong the systemic circulation of the particulate system. PEGylation of nanoparticles defends the surface of the nanoparticles from protein absorption which leads to aggregation, opsonization, and phagocytosis, thereby providing extended systemic retention [52, 89]. The resultant elimination is due to phagocytosis by the monomolecular phagocyte system. Because of the large number of phagocytic cells in the liver and spleen, the majority of opsonized particles are removed by a receptor-mediated mechanism in less than a few minutes, or they are expelled. Thus, numerous approaches are explored by the investigators to help retain the nanoparticles in the systemic circulation, so that drug delivery system can deliver the drug for prolonged period of time with specific distribution [9, 12, 83]. The effects of physiological tissue deficits and polymeric nanoparticle physicochemical characteristics on clearance and biodistribution will be discussed in this chapter to consider probable means for their advancement.

2 Pharmacokinetic Functions

Investigators have explored various factors such as physicochemical properties, administration route, dosing, and coating, affecting distribution and clearance of nanoparticles. However, all these variables are dependent on the physiological environment. Optimization of such variables after understanding of pharmacokinetics of body will help to obtain the successful drug delivery using polymeric nanoparticles.

Briefly, once the nanoparticles are introduced into systemic circulation, they are distributed to various tissues and organs where they are encountered with physical and biological challenges that may change their properties and affect their deposition and are concurrently cleared later [85] (Fig. 14.1). The interactions between nanoparticles and each organ are unique. In vivo, the major clearance process for polymeric nanoparticles is reticular endothelial system (RES) also termed as mononuclear phagocyte system (MPS) [13, 75]. Phagocytosis of polymeric nanoparticles is usually initiated by opsonization process. Opsonization occurs when opsonins, a heterogeneous group of proteins or protein fragments including C3, C4, and C5, immunoglobulins, fibronectin, and apolipoproteins, are deposited on the surface of nanoparticles and interact with a variety of surface receptors on RES cells, including complement, Fc, and fibronectin receptors [4, 71]. Proteins other than opsonins also get attached on the surface of nanoparticles forming a corona which further enables the scavenger receptors to categorize [80]. This adds an alternative way by which RES clears polymeric nanoparticles. Once

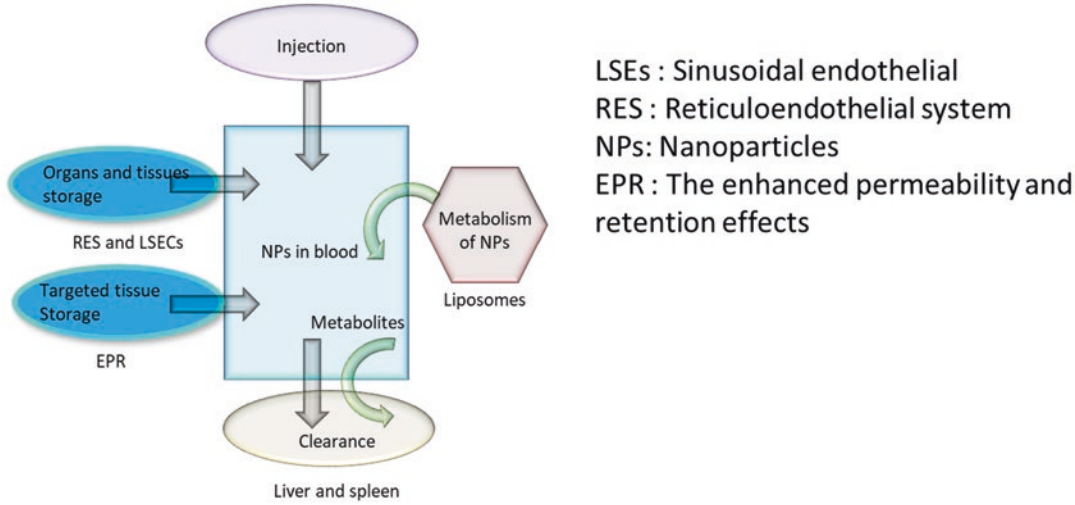

Fig. 14.1 Schematic diagram illustrating biodistribution and clearance of polymeric nanoparticles

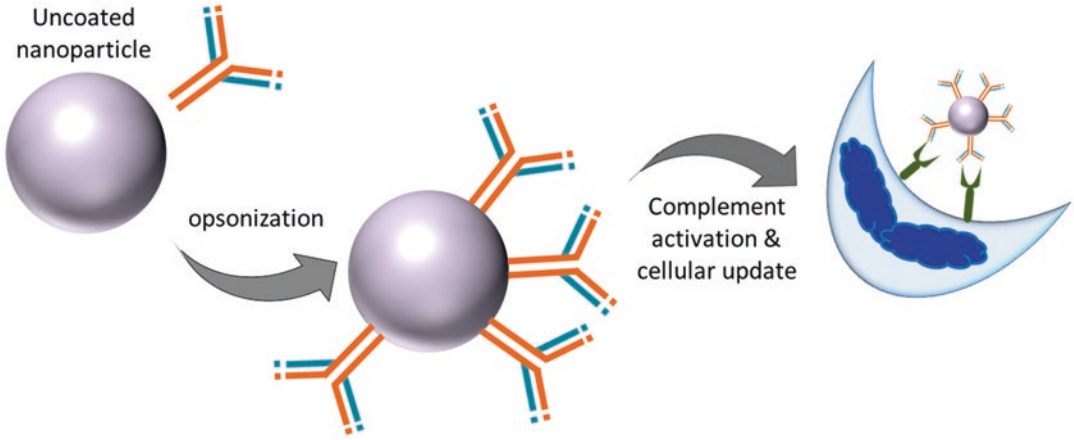

Fig. 14.2 Opsonization and uptake of uncoated polymer nanoparticles

opsonized and transported from the systemic circulation, a polymeric nanoparticle is usually localized in one of the MPS organs, mainly the liver and spleen [62] (Fig. 14.2). There are numerous such biological barriers naturally designed to safeguard the human body from foreign material. Among these barriers are the immune system's cellular and humoral arms, as well as mucosal barriers. Nanoparticles must overcome such constraints in order to reach their desired target. Nanoparticles are exceptionally well adapted to overcoming these limitations due to their nanoscale size and ability to surface functionalize to encompass desired properties.

Important nutrients, oxygen, and other molecules are transported throughout the body via blood vessels. Circulatory system plays an important role in continuous transportation of materials in the body. The endothelium of the blood vessels has been classified as continuous, fenestrated, or discontinuous (sinusoidal), depending on the arrangement of cells. Arteries and vessels of the brain, lungs, skin, and heart have continuous endothelium. Fenestrated endo-

thelium is found in capillaries of exocrine and endocrine glands, gastric and intestinal mucosa, choroid plexus, glomeruli, and a subpopulation of renal tubules (fenestrae of approximately 70 nm in diameter). Discontinuous endothelium is found in certain sinusoidal vascular beds, most particularly the liver with fenestrations of 100–200 nm in diameter [1]. Blood vessel endothelial cells can react to the physiological conditions, culminating in angiogenic activity. The creation of new blood vessels is known as angiogenesis. Endothelial cells, which line the inside walls of blood arteries, migrate, proliferate, and differentiate during this process. Chemical impulses in the body influence the process of angiogenesis. Angiogenesis results in a weak lymphatic drainage system and a faulty hyper-vasculature during tumor growth [60]. These openings help the passive movement of nanoparticles to target tumors through the enhanced permeability and retention effect (EPR) [41], wherein the macromolecules or nanoparticles accumulate and diffuse into tumor tissue releasing the therapeutic drug locally [5, 6, 26].

3 Factors Affecting Biodistribution and Clearance of Nanoparticles

Over the last few years, research investigators have developed various types of nanoparticles with exclusive functions and characteristics for targeting purpose. Characteristics such as different therapeutic or imaging functions, special drug loading and release competences, particle sizes, type of materials, different surface charges, hydrophilic or hydrophobic properties, biodegradability, biocompatibility, and different molecular-targeting capabilities aid the nanoparticles to achieve the desired performance. However, among all the listed properties of nanoparticles, only four factors are considered to be critical for their biodistribution and clearance, namely, particle size, shape, surface charge, and surface modification. Table 14.1 demonstrates various polymeric nanoparticles and the factors associated with their pharmacokinetics. Figure 14.3 illustrates various forms of polymeric nanoparticles.

Table 14.1 Factors affecting pharmacokinetics of various polymeric nanoparticles

Polymeric nanoparticles	Pharmacokinetics	Factor	Reference
PLGA/polyvinyl acid nanospheres	Hepatic uptake	Particle size: 200 nm	Di Mascolo et al. [23]
PLAcore/PVAshell nanoparticles	Hepatic uptake	Particle size: 273.1 nm	Canup et al. [8]
Chitosan	Hepatic uptake	Particle size: 210–279 nm	Xiao et al. [88]
Polyethylenimine nanoparticles	Hepatic uptake	Particle size: 150–200 nm	Iranpur Mobarakeh et al. [39]
Polymeric nanoparticle	Lung and spleen uptake	Shape: Rod	Kolhar et al. [46]
Copolymer of poly[(ethylene glycol) methyl ether methacrylate] and poly(glycidyl methacrylate) nanoparticles	RES uptake	Shape: Cylinder Particle size: 35–1200 nm	Müllner et al. [58]
Glyceryl monostearate nanoparticles	Spleen uptake	Particle size: 350–500 nm	Patil et al. [64]
Carboxylated polystyrene nanoparticles	Lungs uptake	Surface modification: ICAM-antibody-coating	Anselmo et al. [2]
Phosphatidylcholine/cholesterol liposomes	Liver uptake	Surface charge	Levchenko et al. [50]
PLGA nanoparticles	Tumor uptake	Surface modification with chitosan or Eudragit® RS 100	Kırımlıoğlu and Görgülü [44]
Polystyrene nanoparticles	M1 macrophage uptake reduced	Surface modification with PEG	Qie et al. [68]
PEG-b-PLA nanoparticles	Tumor uptake enhanced	Positive charge	Wang et al. [81]

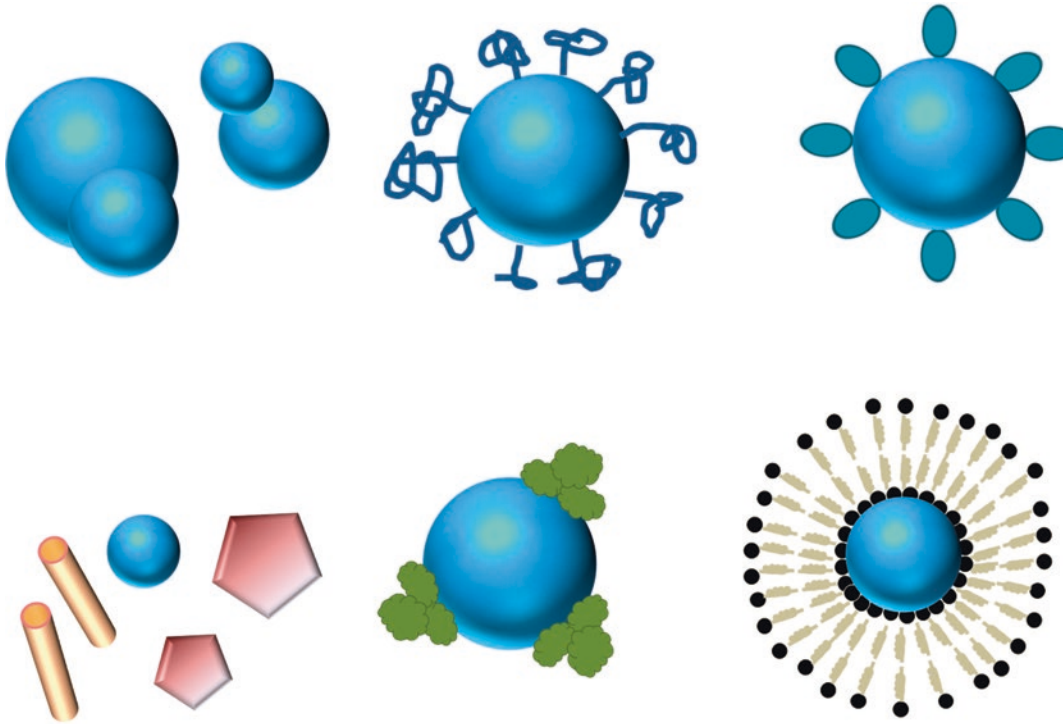

Fig. 14.3 Various shapes and surface modifications of nanoparticles

3.1 Particle Size

It is obvious, based on physiological characteristics including hepatic filtration, tissue extravasation, tissue diffusion, and kidney excretion, that the size of the nanoparticles has a significant impact on their distribution and clearance. The systemic life of employed nanoparticles in blood is determined by not only the organs' clearance efficiency, their ability to target tumors using the EPR effect, and the degradation duration in the blood, but also the particles' physicochemical features. Thus, as one of the most important attributes of a nanoparticle, size should be addressed first when tailoring drug loading and other therapeutic characteristics. Furthermore, polymeric nanoparticles' aggregation ability in tumors may be reduced if they are removed too quickly, yet too long retention in the body might contribute to greater toxicity. As a result, a nanoparticle size optimization is necessary to improve the applications of nanoparticles.

Circulation half-lives, extravasation through leaky vasculature, and macrophage uptake are all driven by size and have discrete cut-off size ranges. Various researchers have investigated optimized nanoparticle size for systemic retention resulting in desired therapeutic efficacy. From the studies, it is concluded that particle size less than 6 nm are easily filtered out through the kidney [16, 54]. In one study, in vivo biodistribution results of PLGA nanoparticles with consistent composition and particle size 160 nm showed intrahepatic delivery and therapeutic efficacy [48]. In another study, the in vivo spleen administration of the degradable poly(amine-co-ester) nanoparticles encapsulating siRNA protein with a size of 240–300 nm allowed up to 60% Nogo-B protein suppression [17]. Particles in the micrometer range have been demonstrated to efficiently aggregate within pulmonary capillaries, potentially providing a special benefit when targeting among the most major intersections of metastatic malignancy [32]. Pore sizes in leaky tumor vasculatures have been observed to range between

380 and 780 nm [35, 93]. Thus, due to the EPR effect, only nanoparticles smaller than 600 nm can be employed. In one study, PLGA nanoparticles encapsulating curcumin were investigated for cellular uptake by cervical cancer cells. Results demonstrated that polymeric curcumin nanoparticles of 132 nm in size were targeted to P-glycoprotein on the cell surface membrane of KB-V1 cells [67]. Drug carriers' size has a significant impact on their in vivo circulation time. It is found that as particle size increases, in vivo circulation time also increases [65]. This does not, however, imply that an unlimited increase in particle size leads to an infinitely long in vivo circulation duration. If merely considering the size difference in nanoparticle clearance, nanoparticles with diameters between 100 and 200 nm are more acceptable for utilization since they have a longer blood circulation and a lower rate of MPS absorption [47, 86, 94]. However, the size of nanoparticles is determined by the desired properties of nanoparticles and their application significance. For instance, a few smaller nanoparticles have been developed by some investigators because of their ease of clearance, which reduces the risk of chronic toxicity, or their high infiltration and retaining behavior, which improves the targeting outcome [20].

3.2 Particle Shape

The spherical shape of nanoparticles is the most frequent since it has the fewest dimensions and is the easiest to make. Diverse forms of nanoparticles have been found to have a major impact on their biodistribution and clearance, giving specific roles in medical applications. Wire [38], sphere [25], ellipsoid [21], rod [18], cylinder [37], sheet [94], cube [56], needle [45], and cluster-like [11] nanoparticle forms have been identified. The effect of shape of nanoparticles can be traced to a variety of factors. For instance, it is observed that nanoparticles with irregular shapes were more likely to settle in the spleen [22].

Various investigators have reported selective uptake of spherical nanoparticles by MPS over rod-shaped counterparts [14, 15]. Li and coresearchers reported that cellular uptake of nanoparticles was in the sequence of sphere > cube > rod > disk in an in vitro cell uptake examination of various shaped PEGylated nanoparticles. This is likely owing to the ease of folding the cell membrane around the particles [51]. The oblate form of particles helps them circulate in the bloodstream because macrophages have lower uptake [72]. Intravenously injected filamentous micelles lasted ten times longer in circulation than spherical polymersomes, lasting up to 1 week [27]. Rod-like camptothecin-conjugated PEGylated dendrimers [99] showed faster cell uptake in vitro and longer circulation half-life along with high tumor uptake in vivo as compared to nanospheres. In one study, the renal system efficiently cleared single-walled carbon nanotubes with rod lengths ranging from 100 to 500 nm and diameters of 0.8–1.2 nm; driven by flow-induced orientation, the rods' long-axis went readily through the glomerular capillary fenestrations [70].

3.3 Surface Charge

Remarkably, certain nanoparticles' surface physicochemical characteristics can alter when used in vivo, modifying biodistribution and clearance. It has been proven that a polymeric nanoparticle's physicochemical attributes, such as surface charge and functional groups, can influence its uptake by phagocytic cells. For instance, when compared to neutral or negatively charged formulations, positively charged nanoparticles have a higher rate of cell uptake. In a study, less negatively charged rhodamine B-carboxymethyl chitosan-grafted nanoparticles and more positively charged rhodamine B-chitosan hydrochloride-grafted nanoparticles were tended to be more efficiently internalized by both L02 and SMMC-7721 cells, suggesting that surface charge played an important role in cellular uptake of polymeric nanoparticles [33]. In most situations, the nanoparticle surface contributes the driving forces for cellular internalization (electrostatic, hydrophobic, and hydrophilic (polar)

forces) and determines the uptake pathway. Nanoparticles with a positively charged surface are projected to have a high nonspecific internalization rate because of their effective binding to negatively charged groups on the cell surface and tend to have a short half-life in the bloodstream [63, 79, 94, 95]. Furthermore, an excess of positive charge on the complexes can result in nonspecific binding and absorption by cells that are not targeted. For complexes containing a targeting ligand, a weekly positively charged surface is desirable for receptor-mediated endocytosis selective binding. In a study, an amphoteric hyaluronic acid derivative with polyethylenimine chains for gene delivery overcome the disadvantages of polyethylenimine as gene carrier including the cytotoxicity caused by excess of positive charge, non-special interaction and aggregation in the blood, and non-target gene delivery [92]. In another study, effect of surface charge on the cellular uptake and in vivo fate of PEG-oligocholic acid-based micellar nanoparticles was reported. After opsonization in fresh mouse serum, RAW 264.7 murine macrophages took up nanoparticles with a high surface charge, whether positive or negative. In vivo biodistribution experiments revealed that strongly positively or negatively charged nanoparticles had very high liver absorption, which is likely owing to active phagocytosis by macrophages in the liver [87].

3.4 Surface Modification

Due to the ease of detection by the RES, most uncoated nanoparticles can be swiftly removed from blood circulation when utilized in vivo, resulting in a significant loss in targeting ability [76]. Surface functionalization of nanoparticles mainly comprises PEG, the negative carboxyl (–COOH) group, neutral functional groups like hydroxyl (–OH) groups, and the positive amine (–NH2) group. The increase in (–NH2) resulted in a higher positive surface charge, which increased the cellular uptake of nanoparticles [55]. Rate of blood clearance of non-PEGylated nanoparticles is found to be more than PEGylated nanoparticles. PEGylation provides stealth properties to the nanoparticles surface protecting further from uptake by MPS (Fig. 14.4) [24, 91]. In one investigation, in vivo study in ICR mice showed polyethylene glycol and heparin (PEG/

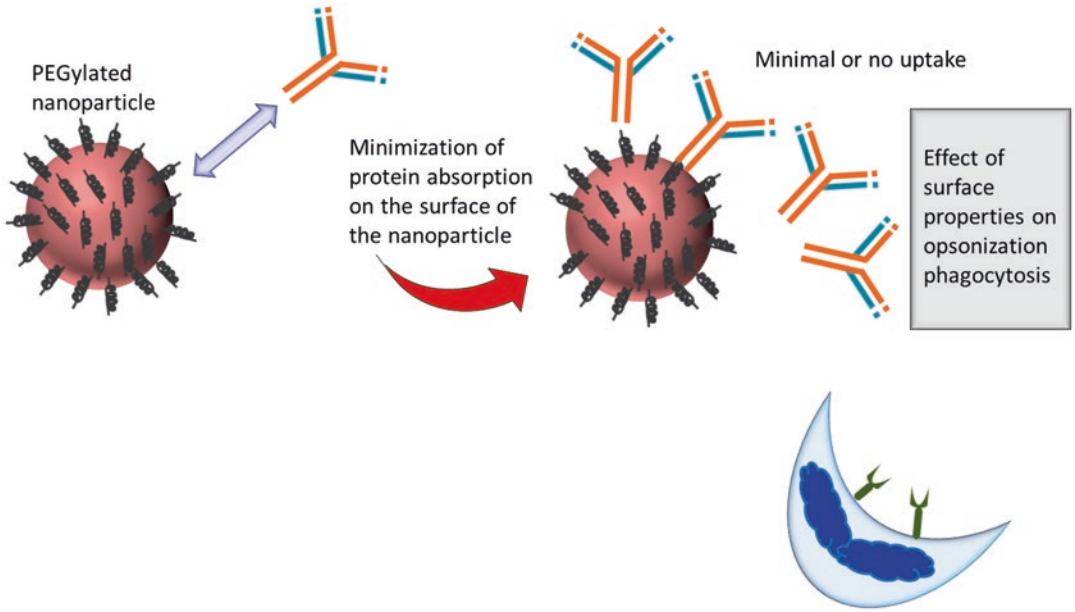

Fig. 14.4 Effect of PEGylation on nanoparticle pharmacokinetics

HEP) coating increased the blood circulation half-life of lipid polymer hybrid nanoparticles (LPHNPs) from 0.3 to 72.6 h. Moreover, PEG/HEP LPHNPs exhibited dramatically reduced liver accumulation when compared to LPHNPs [73]. In a similar study, researchers had developed polyethylene glycol and human serum albumin coating of nanoparticles carrying resveratrol for pancreatic tumor therapy. The surface-modified nanoparticles demonstrated prolonged blood circulation approximately 5.43-fold [28]. Doxorubicin-loaded nanoparticles based on polyethylene glycol-conjugated chitosan oligosaccharide-arachidic acid were explored for potential application to leukemia therapy. Results illustrated higher uptake of the conjugated nanoparticles by K562 cells with slower in vivo clearance rate, subsequently extending the blood circulation [77].

4 Conclusion

The development of a complete concept of nanoparticle pharmacokinetics in order to recognize their distribution and clearance is influenced by physiological factors and nanoparticle component such as particle size, shape, surface charge, and modification. Various investigators have been studying these characteristics since long time. Because the interactions between nanoparticles and the body are so complicated and variable, it is important to understand and follow past knowledge and principles for nanoparticle design.

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