CHAPTER

Pharmacokinetics and pharmacodynamics of the advanced drug delivery systems

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1 Pharmacokinetics

The term pharmacokinetics is composed of "pharmakon" and "kinetics." Pharmakon is a Greek word, referring to "drugs and poisons," and kinetics denotes "alternations in variables with respect to time" [1, 2]. Thus pharmacokinetics is a branch of science encompassing what a living body does to a drug molecule and deals with the absorption, distribution, metabolism, and excretion of drugs both in human and animals [3]. In addition, pharmacokinetics also copes with drug dosing calculations, in vitro/in vivo correlation, determination of bioavailability, and bioequivalence toxicity studies and assessment of drug interaction.

1.1 Pharmacokinetic models

The main goal of pharmacokinetic modeling is to determine the prominent characteristics of a drug following the in vivo administration. This provides not only the evaluation but also the intensity of a drug's action and its duration investigated under the pathological and physiological conditions [4]. The pharmacokinetic models could be regarded as either empirical or explicative (mechanistic). Empirical models are primarily based on mathematics involving the study of drug concentration in a given specimen of biological organ or fluid over the time. On the contrary the explicative models involve the anatomical hypotheses about pharmacokinetics. Therefore the general compartmental models are regarded as explicative because they divide a living body into various compartments or zones for the absorption, distribution, and elimination of the administered drug [5, 6]. Physiologically based models are also categorized as mechanistic models. Apart from the classical compartmental modeling approach, the noncompartmental modeling approach is also emerging.

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1.1.1 Compartmental modeling

Compartmental modeling is among the most employed approaches in pharmacokinetics. This approach is based on the assumption of a compartment as a tissue or a combination of tissues with closely identical blood perfusion and drug affinity. The drug distribution is assumed uniform within a compartment, and in addition, the absorption of the drug within a compartment is regarded spontaneous and homogeneous so that the drug concentration corresponds to a standard and reproducible concentration with every drug molecule possesses similar chance of exiting the compartment. The rate constants are employed to indicate the net rate of drug penetration into and excretion from the compartment [7]. This approach describes a living body as an existence divided into one or numerous compartments. Being administrated into a body, firstly, the drug penetrates the central compartment (absorption), followed by its transfer into the peripheral compartments (distribution) and irreversible elimination from the central compartment (biotransformation and excretion). Fig. 1 depicts the classical one-compartment pharmacokinetic model.

1.1.2 Noncompartmental modeling

The noncompartmental pharmacokinetic modeling approach is scantily organized than traditional pharmacokinetic modeling approach [8]. The noncompartmental modeling involves the estimation of various pharmacokinetic parameters by avoiding the monotonous and illusive methodologies of nonlinear regression (i.e., it is assumed that the drug follows a linear pharmacokinetics). The noncompartmental modeling methods are promptly mechanized and thus minimize human error and intervention. For instance, it is convenient to estimate the area under the curve (AUC), area under the first moment curve (AUMC), and mean residence time (MRT) than to automate the parameter estimation of classical compartmental modeling approach, though efforts have been made, for instance, AUTOAN that is a pharmacokinetic computer program [9].

1.2 Pharmacokinetic parameters

This section describes the various pharmacokinetic parameters such as elimination rate constant, the volume of distribution, half-life, and clearance using the one-compartment open model system.

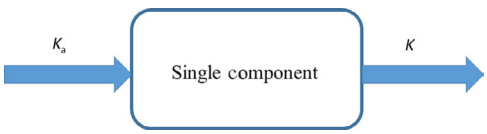

FIG. 1

One-compartment pharmacokinetic model. k_a, absorption rate constant (h^{-1}), and k, elimination rate constant (h^{-1}).

1.2.1 Elimination rate constant

Assume a single intravenous (IV) bolus injection of drug *X* (Fig. 2). With time the concentration of drug in the body decreases. Thus the rate of elimination can be described (considering the first-order elimination) as follows:

$$dX / dt = -kX \tag{1}$$

Hence

$$X = X_0 \exp(-kt) \tag{2}$$

where X, the amount of drug at each time (t); X_0, the injected dose; and k, first-order elimination rate constant [10].

1.2.2 Volume of distribution

The volume of distribution (V_d) is not a "real" volume and rather an apparent volume of distribution. It refers to the volume of plasma available for the dissolution of a drug in the body to indicate the drug concentration acquired in plasma. The living body is a heterogeneous unit, even then a one-compartment model is employed to estimate the plasma concentration-time profile of numerous drugs. It is pivotal to remember that the drug concentration (C_p) in blood plasma may not be the same as in the kidneys, liver, or other tissues. Consequently, C_p in blood plasma is not equal to C or amount of drug (X) in the kidney or C or amount of drug (X) in the liver or C or amount of drug (X) in tissues. Nevertheless, the alterations in the drug concentration in human plasma (C_p) are proportional to the variations in the amount of drug (X) in the tissues (i.e., the body). As it is evident:

$$C_p\,(\text{plasma}) \simeq C\,(\text{tissues}), \text{ i.e., } C_p\,(\text{plasma}) \simeq X\,(\text{tissues}) \tag{3}$$

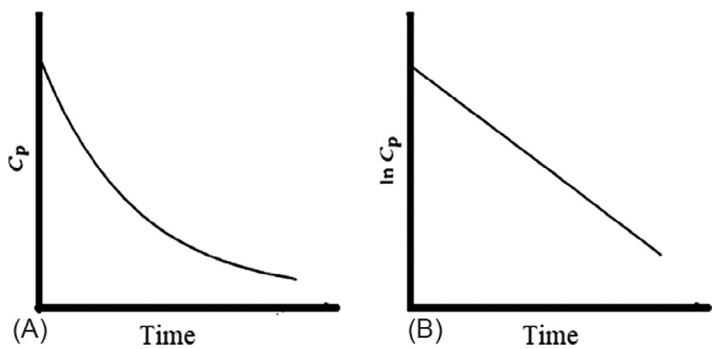

FIG. 2

One-compartment pharmacokinetic model: (A) plasma concentration (C_p) versus time and (B) log C_p versus time.

Then

$$V_d C_p = X \tag{4}$$

where X is the total amount of drug in the body and V_d is the constant of proportionality and is considered as the volume of distribution, which therefore denotes the total amount of drug in the body at any time to the respective plasma concentration. Thus,

$$V_d = X / C_p \tag{5}$$

and V_d can be employed to convert the drug amount "X" to concentration. Since

$$X / X_0 = \exp(-kt) \tag{6}$$

Then

$$X / V_d = X_0 \exp(-kt) / V_d \tag{7}$$

As

$$C_p = X / V_d \tag{8}$$

$$C_p = C_0 \exp(-kt) \tag{9}$$

Eq. (9) indicates a monoexponential decay where C_p is the plasma concentration at any time (t). If a drug has a large V_d, which does not reflect the total plasma volume, it indicates that the drug is enormously distributed in tissues. On the contrary, if V_d is closely similar to the total blood plasma volume, then it is likely that the total dose of the drug is not widely distributed, corresponding to a robust concentration mainly in the plasma [11, 12].

1.2.3 Half-life

The half-life is defined as the time within which the drug plasma concentration is diminished to one-half of its original concentration ($t_{1/2}$). This pharmacokinetic parameter is quite helpful to assess the approximate time taken for the drug concentration to be decreased by half of the original one. In addition, the half-life is also employed to calculate the stoppage time if a patient possesses toxic drug content, provided the drug exhibits linear one-compartment pharmacokinetics [13].

1.2.4 Drug clearance

Drug clearance (CL) refers to the volume of plasma in the vascular tissues cleared of drug per unit time by the processes of biotransformation and excretion. The drug clearance is constant if the elimination is following the first-order kinetics. Drug clearance happens either by renal excretion or by biotransformation or both. Thus clearance is estimated as follows:

$$\mathrm{CL}_{\mathrm{total}} = \mathrm{CL}_{\mathrm{renal}} + \mathrm{CL}_{\mathrm{nonrenal}} \tag{10}$$

Drug clearance is the result of the first-order elimination rate constant (k) and the apparent volume of distribution (V_d). Drug clearance is dependent on half-life; for instance, if a drug has a CL of 1 L/h, this tells you that 1 L of V_d is cleared of drug per hour. If the C_p is 20 mg/L, then 20 mg of the drug is eliminated per hour [13].

2 Pharmacodynamics

Pharmacodynamics evaluates the physiologic molecular and biochemical effects or actions of a drug. It is derived from the Greek words "pharmakon" meaning drug and "dynamikos" meaning power. Drugs induce the therapeutic responses by interacting with biological targets at the molecular level to produce an alteration in targeted molecule activity following the intermolecular interactions. Some of these molecular interactions include postreceptor effects, receptor binding, and chemical interactions. For instance, the binding of drug to an active position of an enzyme, the interaction of drugs with cell membranes triggering the proteins to disturb the downstream signaling, and drug binding at tumor necrosis factor (TNF) [14]. Following the drug-target interaction, responses become pronounced, which can be evaluated biochemically or clinically. For instance, the obstruction of platelet clumping after the administration of aspirin, decrease of blood pressure after diuretics and the hypoglycemia following the insulin intake. Though these examples are evident for the action of the preceding drugs, the administration of drugs should be done with caution so that these drugs are not merely delivered not only to impede platelet aggregation, minimizing blood pressure or reducing blood glucose, but also to mitigate the probabilities of cerebrovascular diseases, myocardial infarction, and renal issues via the drug's pharmacodynamics [15].

A few basic concepts and terms are employed to elaborate pharmacodynamics and to describe the intensity and period of a drug's response. For instance, E_{max} refers to the maximal effect of a drug on a disease under investigation. For example, E_{max} could be a marker of platelet inhibition as a test ex vivo or the maximum reduction in hypertension. EC_{50} refers to the concentration of the drug at a stable state inducing half of the maximum effect. Hill coefficient is the slope of the relationship between drug concentration and its therapeutic response. A Hill coefficient value above 2 shows a steep relationship (i.e., very small alterations in concentration induces splendid magnitude in response), and Hill coefficient value above 3 corresponds to nearly instantaneous "all or none" effect [16].

3 The pharmacokinetics and pharmacodynamics profiling

As aforementioned, pharmacokinetics (PK) monitors the time course and concentration of a drug molecule involving absorption, distribution, metabolism, and excretion in the body (Fig. 3). A pivotal indicator of PK is the bioavailability that refers to the net amount of a delivered drug dose in its active unchanged form reaching the blood apart

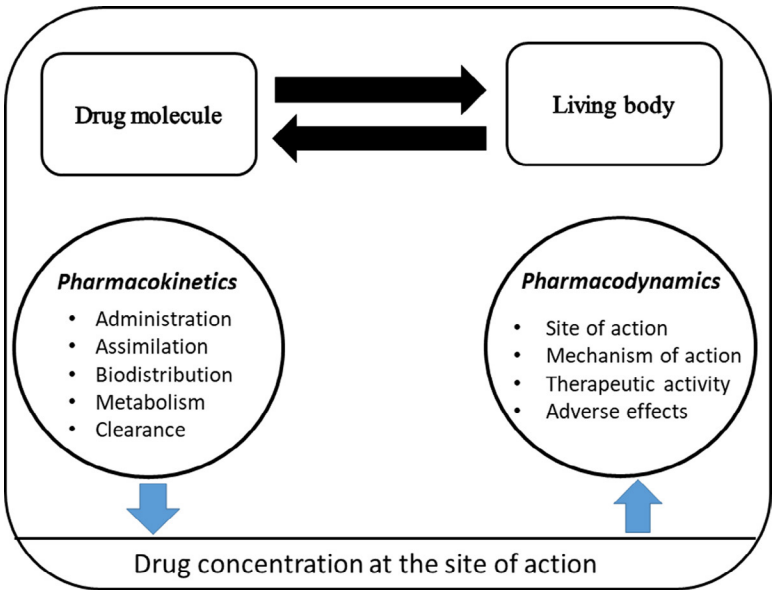

FIG. 3

The correlation between pharmacokinetics and pharmacodynamics.

from intravenous administration. This is because upon intravenous administration, the drug bioavailability is 100%; however, all other routes of administration render less than 100% bioavailability owing to partial absorption and hepatic biotransformation and fluctuate from person to person. Consequently, pharmacokinetics has been employed clinically over the years to standardize the therapeutic performance of drug molecules [17, 18]. On the contrary, pharmacodynamics indicates the correlation between the drug concentration available at the site of action and the corresponding therapeutic effect, including its duration, intensity, and unwanted effects (Fig. 3). In addition to concentration, the response of a drug available at the site of action is also influenced by a drug's adherence with a biological target. In general the higher the concentration of a drug molecule at the biological target, the higher the intensity of its therapeutic response. Thus there is a strong correlation between the concentration of a drug at the biological target and its pharmacology. During the pharmacodynamics studies, E_{max} and the drug potency (EC_{50}) (50% effective concentration) could be estimated by simply correlating the plasma drug concentration with therapeutic effect. Apart from that, another aspect that pharmacodynamics can yield is the tolerance that indicates a reduction in therapeutic drug response upon its prolonged intake. The tolerance could arise owing to both pharmacokinetic and pharmacodynamic aspects, and therefore the integration of pharmacokinetics and pharmacodynamics is pivotal. Consequently, various models have been devised and used to anticipate the concentration versus time profiles for various dosing manipulations [18]. The estimation of pharmacokinetics/pharmacodynamics is particularly quite important in pregnant women, elderly, and children.

The mathematical models can also forecast the possible correlation between the drug concentration and its therapeutic efficacy prior to in vivo studies. Although the clearance denotes the capability of the body to eliminate the administered drug, it does not reflect the exact amount of drug eliminated [10]. Bioavailability refers to the fragment of a delivered drug reaching the site of action following the absorption. The bioavailability is estimated by comparing the area under the curve (AUC) acquired from the plasma concentration versus time curve following the intravenous (AUC_{IV}) and various alternative routes of drug administration [19, 20]:

$$\text{Bioavailability} = \text{AUC} / \text{AUC}_{\text{IV}} \tag{11}$$

The half-life ($t_{1/2}$) is the time that takes for the plasma drug concentration to decrease by 50% and is typically calculated from the following equation:

$$t_{1/2} = 0.693 / k \tag{12}$$

where k is the elimination rate constant ($K = \text{CL}/V_{\text{d}}$).

4 Advanced drug delivery systems

During the 1970s controlled drug delivery systems (DDS), capable of delivering the drug molecules in a planned and predicated manner of time at predetermined rates, enticed enormous interest [21, 22]. With the innovation and developments, advanced drug delivery has emanated as an area capable of targeting micro/macro-drug molecules or genes to the intended tissues or organs. The primary aim of a targeted delivery system is to transfer an adequate quantity of an active ingredient to the identified locations (such as afflicted tissues and tumors) while mitigating the unwanted effects on normal organs or tissues [23]. Micro- and nanosized advanced drug delivery systems are capable of enhancing the therapeutic performance in the management of various ailments owing to rapid detection and timely response directly at the diseased site. This novel field of advanced drug delivery system denotes to intelligent and responsive delivery systems fabricated to carry out numerous tasks such as identification, targeting/or delivery of a drug molecule for the management of pathological conditions [24]. Nanotechnology is regarded as the advanced drug delivery system of the upcoming era. In the design of a nanotechnology-based drug delivery system, the following pivotal requirements must be met, namely, size range between 1 and 100 nm and possessing essential command over the physicochemical features of molecular-level scaffolds [25]. Nanotechnology has been employed in medicine for the targeted drug delivery leading to upgradation in the treatment options available for a variety of disorders and diseases.

In this chapter the pharmacokinetics and pharmacodynamics of advanced drug delivery systems such as nanotechnology encompassing micelles, polymeric nanoparticles, dendrimers, and polymeric carbon nanotube will be discussed.

5 Nanotechnology-based advanced drug delivery systems

Nanotechnology involves the development of nanoparticles (NPs) with sizes range in the nanoregion (1–1000 nm). The NPs have chief merit over atoms and molecules owing to their larger surface area per unit volume. In addition, NPs offer better flexibility in fabrication in terms of numerous shapes and sizes with varied chemical surface attributes. Owing to flexible nature, NPs can be employed both as therapeutic and diagnostic tools. Some of the nanotechnology-based advanced drug delivery systems are micelles, polymeric nanoparticles, lipid-based nanoparticles, inorganic nanoparticles, metal nanoparticles, mesoporous silica systems, dendrimers, polymeric carbon nanotube, and nanoemulsions (Fig. 4). Nevertheless, the size up to 220 nm is recommended for the clinical use because of usage of a standard 0.22-μm (220 nm) filter medium prior to NP injection into the body. Although nanotechnology offers immense advantages both in biomedical applications and nanomedicine, a limitation still exists on the comprehension and the process of pharmacokinetics and pharmacodynamics of NPs. An optimal nanotechnology-based advanced drug delivery system should acquire numerous attributes such as exertion of action solely on the target areas with robust drug release kinetics in therapeutically effective

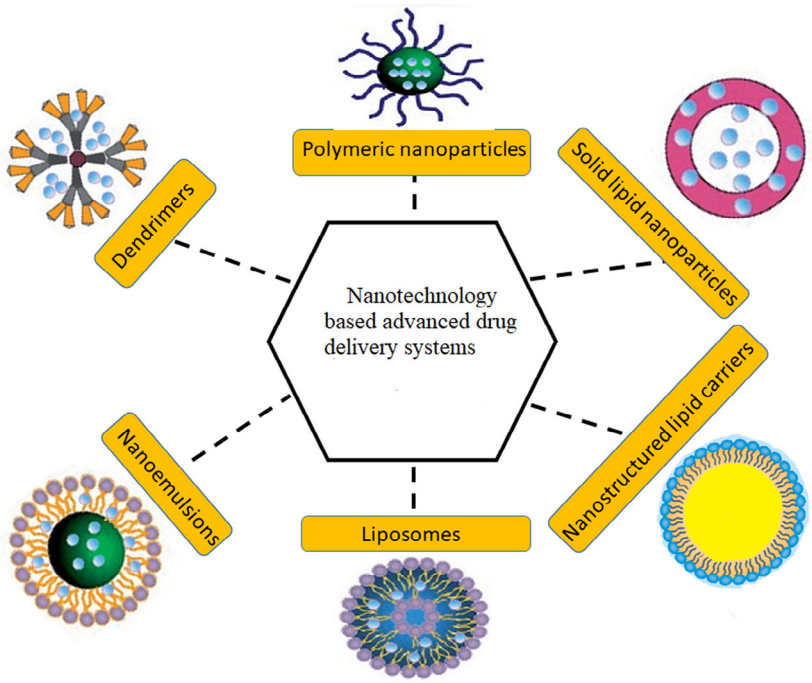

FIG. 4

The various types of nanotechnology-based advanced drug delivery systems.

concentrations. Acknowledging the increasing usage of NPs in cancer therapy [26, 27] and that the in vivo performance of NPs are primarily influenced by their pharmacokinetics (PK) and pharmacodynamics (PD), a brief review of these two aspects is being provided in this chapter.

6 Pharmacokinetics of NPs

The physicochemical characteristics of NPs play a pivotal role in regulating their PK as they influence the prompt therapeutic action upon the administration NPs into the body. The low bioavailability of a drug molecule could be enhanced by promoting the drug dissolution rates using "nanosizing" of a formulation. In addition, nanosizing could also extend the biological half-life of therapeutic agents leading to a delay in their clearance or degradation. Numerous factors that can alter the PK of NPs are described. The pharmacokinetics of nanotechnology-based advanced drug delivery systems encompasses four major aspects, namely, absorption, biodistribution, biotransformation, and excretion [28, 29].

6.1 Absorption of NPs

Absorption or assimilation process involves the entrance of a drug molecule into the blood following the administration. The absorption of NPs has been investigated using numerous routes of administration such as oral, nasal, pulmonary, percutaneous, and parenteral [29] and is being discussed in the following section.

6.1.1 Oral adsorption

Following the oral administration the NPs can either be absorbed into the blood circulation or could be excreted through the feces [30]. There are two prominent obstacles for the absorption of drugs encapsulated in the NPs, namely, the epithelium and the mucus of the gastrointestinal system (GIT). Numerous documented studies have reported the absorption of NPs having a size range of 50 nm–200 mm via Peyer's patches located in the small intestine [31]. In addition, the absorption of NPs via intestinal enterocytes has also been reported [32]. Generally, NPs are bound to gastrointestinal mucosa, thereby promoting their absorption probability [33]. NPs such as spontaneous emulsifying systems (SES) trigger the lymphatic absorption and thus are quite appropriate for drug molecules prone to extensive first-pass metabolism [34]. Similar to SES, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are also having the inherent characteristics of penetration via the lymphatic system and thus evading the first-pass effect. Nevertheless, SLNs and NLCs are also considered to be better than SES for the maintenance of therapeutically effective drug concentration [35, 36]. The design and composition of polymeric nanoparticles can ensure the intended attributes. For example, NPs composed of acid-soluble Eudragit E100 polymer can facilitate the absorption of an administered drug from the gastric mucosa, even at relatively elevated content than that obtained from cyclodextrin complexes [37].

6.1.2 Nasal absorption

Several studies conducted using NPs on animals have indicated the disposition of NPs in the olfactory region, thereby possessing smooth entrance to the brain [38]. The nasal route is extensively used to bypass the blood-brain barrier (BBB). Nonetheless, most of the information is obtained using the animal models, and owing to the substantial variations in the biological and physiochemical nature of human and animal nasal mucosa, investigation using human volunteers is imperative.

6.1.3 Pulmonary absorption

The absorption of NPs administered through the pulmonary route usually encounters two emulous processes, namely, nonabsorptive excretion and absorption [39]. The alveoli have a large surface area that promotes the absorption of NPs followed by endocytosis. Consequently, upon absorption from alveoli, NPs have a smooth course to the blood circulation and lymphatic system [38, 40]. Nonetheless the NPs confined to the tracheobronchial regions (the upper respiratory tract) are prone to expulsion by the mucociliary movements. Generally, particles with the size range between 5 and 10 μm can reach the primary bronchi, between 1 and 5 μm can access secondary bronchi, between 1 and 3 μm are settled in bronchioles, between 500 nm and 1 mm can penetrate alveoli, and with size smaller than 500 nm could be exhaled upon expiration [41].

6.1.4 Percutaneous absorption

The interaction of NPs with the skin epidermis is well known and extensively investigated [42]. The absorption of NPs via dermis is facilitated by lymph nodes and the lymphatic system [40]. A schematic representation of NP absorption via dermis is depicted in Fig. 4. The insertion of biocompatible polymers such as phospholipids and polylactic-*co*-glycolic acid (PLGA) in the composition of NPs has been reported to enhance their interaction and integration with the lipophilic segment of skin, and NPs particularly liposomes having a diameter less than 600 nm have been shown to solely infiltrate the skin [43, 44]. Lipid-based nanoparticles such as SLNs and NLCs with less than 200-nm size constitute a film on the skin and mitigate the moisture loss from the skin surface that leads to untie the packing of corneocytes and thus promotes the intense drug penetration [33, 45]. Polystyrene-based NPs having an estimated size of 20 nm have been demonstrated to pile up in the remote follicular segments, whereas NPs with size range up to 200 nm have been documented to exhibit time-dependent follicular permeation [46]. Some scientific studies have reported that PLGA-based NPs cannot penetrate the stratum corneum; however, polylactic acid (PLA)-based NPs rely on hair follicles and sebaceous glands for percutaneous absorption [47–49]. In a study, magnetic NPs with a size less than 10 nm demonstrated the penetration in the skin layers up to the stratum granulosum [50].

6.1.5 Parenteral absorption

The parenteral absorption of NPs has been demonstrated using numerous injectable routes, such as intramuscular, intradermal, intraperitoneal, and subcutaneous routes. Robust absorption from these injectable routes is a mandatory requirement to initiate

a therapeutic response of a drug molecule. Several mechanisms such as passive diffusion, active transport, carrier-mediated transport, and endocytosis are involved leading to the absorption of NPs administrated via the parenteral route. The absorption of NPs administered via parenteral route is promoted by territorial lymph nodes, macrophages, and dendritic cells [51].

6.2 Biodistribution of nanoparticles

Several investigations have demonstrated the promising biodistribution of NPs in different tissues and organs following their administration from numerous routes. Several features of NPs such as micromeritic, electric, physicochemical, and surface properties together with their interactions with the anatomical barriers and entities dictate the biodistribution profile upon the administration [28, 52]. In general the biodistribution is influenced by some main parameters such as composition, size and morphology, surface charge, and coating.

The drug metabolism chiefly occurs in the liver [53], and most drugs undergo alterations into the more polar metabolites prior to removal using cytochrome P450 and complementary metabolic methods [54, 55]. The composition and surface properties of NPs influence the metabolism profile of the NPs. For instance, NPs composed of lactic acid and glycolic acid (PLGA) are reported to be readily metabolized, and the resultant degraded compounds are employed in various biological cycles such as the Krebs cycle [56]. Nonetheless, alternate NPs such as gold, silver, iron oxide, quantum dots, silica, and carbon are remained relatively intact and are cumbersome to undergo metabolism and consequently can stay in the body for a long duration [57]. For instance, quantum dot NPs have been reported to survive in the body for up to 2 years [40].

6.3 Elimination of nanoparticles

Upon oral administration, drug-loaded NPs are firstly metabolized followed by excretion from the body either by feces or by urine [58]. Nonetheless, renal clearance is the primary route of excretion for majority of extracellular substances. Renal clearance is a complicated process consisting of glomerular filtration and tubular secretion but omitting tubular reabsorption [59]. The tubular secretion is primarily divided into two types, namely, organic acid transport and organic base transport. Salicylates and penicillines are secreted, and uric acid is absorbed by an organic acid transporter. Organic thiazides, quinine, and procainamide are secreted by organic base transporters. In fact, both of these transport systems are bidirectional [7]. Several factors can influence the elimination process such as physiochemical characteristics of the NPs/drug, biodistribution and bioadherence, blood plasma concentration, urine pH, physiological factors, pathological conditions, interactions of NPs/drug, and blood perfusion to kidneys. The chief physiochemical factors altering the renal clearance are particle size, lipophilicity, and pK_a. NPs less than 5.5 nm have the rapid filtration from the glomerulus and thereby are smoothly eliminated. Renal excretion is also quite rapid if a drug/nanoparticle is not bound to a plasma protein. Usually a direct

correlation between the plasma drug concentration and the rate of elimination of a nanoparticle/drug maintains well [60].

6.4 Factors affecting the pharmacokinetics of NPs

Several factors such as size, shape, surface charge, and coating/surface engineering are accounted for the modifications in the pharmacokinetics of the drug molecules/NPs [7].

6.4.1 Size

The NPs with a size smaller than 10 nm and particularly 5.5 nm are promptly filtered via renal filtration or through extravasation, whereas larger NPs have the higher probability of being eliminated by cells of the mononuclear phagocyte system (MPS) [7, 61]. NPs having a diameter of approximately 100 nm exhibit extended residence in blood circulation with a low rate of MPS uptake [29]. There is a study investigating the biodistribution of radioisotope-labeled liposomes with different diameters (30–400 nm) in the blood, liver, spleen, and tumor in mice. The content of intravenously injected liposomes was determined in various tissues following 4 h [62]. It was reported that 60% of the injected liposomes with a size range between 100 and 200 nm were spotted in the blood, whereas the NPs with a diameter of 250 nm or less than 50 nm contributed up to 20% of the whole amount of NPs in plasma. In addition, the distribution of liposomes with approximately 100-nm size was found to be 20% in the liver, and it was noticed that accumulation of NPs in the liver was exceeded upon size reduction below 50 nm. On the other hand, NPs with a diameter above 400 nm exhibited enhanced spleen uptake (40%–50% after 4 h of injection) [62]. In another study the tumor uptake of liposomes ranging from 100 to 200 nm was found to be four times more than the liposomes larger than 300 nm or those smaller than 50 nm [63].

6.4.2 Shape

Apart from particle size, NP's shape is also another vital factor that can influence their residence time in the body, binding, intravascular transport, and disposition at the intended target [60, 63]. The interaction of differently shaped microsized polystyrene NPs with macrophages was investigated. The researchers elaborated the details with the support of Ω (a dimensionless shape-related aspect associated with the length-normalized curvature). The authors reported that NPs possessing Ω 45 degrees (sphere or ellipsoid) were distributed successfully via actin-cup and ring formation, while phagocytosis velocity inversely correlated to Ω (up to 45 degrees). On the contrary, upon $\Omega > 45$ degrees (ellipsoid), internalization was not reported [64, 65].

6.4.3 Surface charge

Usually the surface charge on NPs is described in terms of zeta potential and has been reported to influence the pharmacokinetics and MPS uptake of nanoparticles [60, 61, 66, 67]. It has been shown that the negatively charged NPs (<-10 mV) exhibit elevated MPS uptake, whereas the positively charged NPs (>10 mV) trigger an enhanced immune response. Neutrally charged NPs (within ± 10 mV) have

been reported to have the lowest MPS uptake and thus extended circulation time [63]. It has been reported that the NPs possessing 40 mV exhibited greater than 90% clearance in 10 min, while neutral NPs (10 mV) showed less than 10% clearance in 10 min [68].

6.4.4 Coating and surface engineering

The coating and surface alterations can also influence the pharmacokinetics of NPs. Therefore to increase the residence time and diminish opsonization, a hydrophilic coating has been conducted [60, 63]. Being approved by the FDA and having low toxicity, polyethylene glycol (PEG) polymers are being extensively employed in this regard. It has been reported that the PEGylated liposome-loaded drug exhibited a three-time reduction in MPS uptake, six-time higher area under the curve, and three-time elevated tumor uptake [69]. In addition, the surface alteration of NPs with poloxamer and poloxamine 908 (a tetrafunctional ethylenediamine block copolymer) has enhanced the transit time and mitigated the MPS uptake [70]. In another study the surface modification of NPs by dint of poloxamine 908 and poloxamer 407 diminished the Kupffer cell uptake [49, 71].

7 Pharmacokinetic profile of various NPs

7.1 Metallic NPs

The use of metallic NPs is prevalent in the delivery of vaccines, biological materials, and smaller drug molecules [72]. Several metals such as silver, iron, gold, and metallic salts such as titanium dioxide and zinc oxide have frequently been investigated for the fabrication of metallic NPs. The particle size, shape, surface charge, surface coating, route of administration, animal species, protein binding, and doses are the prominent factors influencing the pharmacokinetics of metallic nanoparticles. For instance, metallic NPs have been reported to have a shorter plasma half-life in mice and rats as compared with monkeys and rabbits. Nonetheless, oral, percutaneous, and pulmonary absorption of metallic NPs is less, but surface modification and coatings have been applied to rectify these issues. Metallic NPs exhibit prominent biodistribution in the body and reside over several weeks. Usually, they are deposited in the liver, spleen, and lymph nodes, which are primarily ascribed to the nonspecific uptake by MPS. Metallic NPs with a diameter smaller than 100 nm can comfortably cross the BBBs and could be coated using neuropeptides. Owing to their extensive accumulation in tissues, biliary and renal clearance of metallic NPs are quite low, but the renal elimination can be promoted by modifying the coatings and surface [73]. Metallic NPs composed of gold and coated with PEG 500 were fabricated and were demonstrated to have high blood residence time. In addition, these NPs were found to be accumulated for more than 7 days in the liver and spleen resulting in apoptosis and acute inflammation in the liver [74]. In another study the biodistribution of silver NPs was investigated, and the authors reported the disposition of these NPs in the liver and spleen amide the whole time period of the study lasting up to 2 months. Nonetheless the silver NPs did not demonstrate any disposition in the brain [75].

7.2 Cationic and anionic NPs

Diversified charged NPs have been exploited in the drug delivery, and usually the charge is produced using substances such as stearyl amine or dicetyl palmitate [76, 77]. Polystyrene was employed to fabricate the cationic NPs leading to enhanced cell permeation and apoptosis [78]. In another study, PEG-PLA and cationic bovine serum albumin were employed to prepare cationic NPs with better tissue uptake by the spleen and liver [79]. The authors also documented enhanced BBB permeation with diminished bioavailability of coumarin 6 [79]. In another reported study, heparin was delivered using PEG-based cationic magnetic nanoparticles, and the authors reported 11-time improved bioavailability [80]. Anionic NPs are now well known for the biomedical applications such as diagnosis and treatment [81]. Nevertheless, cationic NPs are typically chosen to owe to their intrinsic better electrostatic bioadhesion onto the negatively charged mucin [82]. However, the pros and cons of the charged NPs should be carefully evaluated because of the possibility of tissue necrosis and hemolysis [83].

7.3 Functionalized nanoparticles

The modification of the NPs is an approach to acquire sophisticated drug delivery and intended pharmacokinetic outcomes [84, 85]. PEG and polyacrylic acid were employed to fabricate the surface-coated functionalized NPs, and authors reported better plasma half-life, and the NPs were found deposited primarily in spleen and liver [86]. In another study, PEG and PLGA were employed to formulate the functionalized NPs, and the authors reported the intense disposition and robust pharmacokinetics [87]. Thus, in general, the alteration of NPs is carried out to acquire advantages such as enhanced drug loading, circumventing of MPS, prolonged distribution, and tissue targeting [88].

7.4 Targeted nanoparticles

Targeted NPs are particularly designed to be disease specific and target oriented to effectively transfer the drug to the intended location [89]. In a study, researchers employed PEG, PLGA, estimated glomerular filtration rate (EGFR) peptide, and *n* poly (3-caprolactone) to fabricate targeted lonidamine/paclitaxel NPs, and a superior pharmacokinetic profile was found as compared with the commercialized products [90]. In another study, human serum albumin and EGFR peptide were used to prepare the cetuximab NPs with reported enhanced intracellular disposition of targeted NPs [91]. In addition, numerous organic compounds such as nicotinamide, folic acid, and estrogen were used to label the NPs for facilitated transport to the intended area [92].

8 Pharmacokinetics and pharmacodynamics considerations in nanotechnology

Nanotechnology is extensively employed for the specific targeting of numerous drugs with the advantages of enhanced bioavailability, diminished toxicity, maintenance of drug/gene efficacy in the target site, solubilization of drugs for intravascular delivery,

and/or cushioning of the stability of administered drugs against the enzymatic degradation [93, 94]. Owing to these benefits, nanomedicine is emanating as a rapidly developing field [95]. Upon encapsulation in the NPs, the drug is transported at a particular site of the body, thus mitigating its dilution. Consequently, identical therapeutic effect can be obtained using a lower dose [96]. A thorough understanding of physicochemical characteristics of NPs is pivotal to comprehend their biological interactions and activities to substantiate the merits of nanotechnology [97]. Numerous nanoscaled carriers such as liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles or lipid carrier systems, metallic nanoparticles, carbon nanostructures, micelles, and nanoemulsion have been explored as advanced drug delivery systems. The general objective in all these nanocarriers was to alter the PK/PD, enhance the therapeutic performance, and mitigate the drug toxicity. Nonetheless, despite the benefits, NPs possess numerous challenges. For instance, the large surface area resulting from small diameter can induce the particle aggregation, thus exacerbating the physical handling of NPs both in solid and solution form. In addition, large surface area mitigates the drug entrapment efficiency resulting in immediate drug release profile. Overcoming these obstacles is imperative prior to the clinical and commercial application of NPs. Apart from this, nanocarriers can initiate hemolysis, and the prolonged circulating NPs in the blood escalates the interaction time among the NPs and the various blood constituents such as the components of the coagulation system leading to the hyperactivity of the coagulation cascade and blood clotting [98]. Consequently, novel modified NPs are being fabricated to acquire an improved drug formulation with enhanced stability in vivo, high drug entrapment efficacy, controlled release of drug, and precise tissue/organ or tumor targeting.

9 Conclusions and future prospects

Over the past decade, nanotechnology-based advanced drug delivery systems have emerged as one of the potential tools for the targeted and specific treatment of several diseases. However, the therapeutic efficacy of these drug delivery systems primarily relies on their pharmacokinetics and pharmacodynamics. Certain physiochemical characteristics such as design, size, shape, surface charge, and morphology can influence the pharmacokinetics, biodistribution, and pharmacodynamics of NPs. There is a wide range of nanotechnology-based advanced drug delivery systems, and consequently the optimization of design for a particular type may not be applicable to others. Nevertheless, the influence of shape, size, and surface charge/morphology size on the pharmacokinetics could be standardized for all types of NPs. The investigations in both pharmacokinetics and pharmacodynamics domain of NPs are surging, which may provide enhanced comprehension for what the body does to NPs and what NPs do to the body. Nonetheless a gap for further research still persists particularly involving inorganic NPs or NPs comprising relatively noxious substances.

A thorough analysis of pharmacokinetics and pharmacodynamics is pivotal to understand the pharmacological and therapeutic performance of nanoparticles.

The characteristics of materials employed in the composition of NPs have been shown to greatly affect their interaction with the biological membranes and fluids, thus altering the PK and PD of NPs. Consequently, alterations in the NP design and morphology could be done to manipulate their interaction with the biological system, particularly by fabricating the NPs with prolonged circulation time in the bloodstream and better site-specific targeting capabilities. The size of NPs is a quite important parameter as NPs with large size are readily identified by the reticuloendothelial system, which leads to their disposition in the spleen and liver. The surface charge is another crucial attribute of NPs because particles having positive charge show better adherence on a biological membrane and are engulfed more rapidly than the nanoparticles with negative or a neutral surface charge. In addition, NPs having positive surface charge exhibit prompt clearance from the blood and induce numerous repercussions such as platelet aggregation and hemolysis compared with negatively charged or neutral NPs. Nanotechnology has been employed in a drug delivery system for numerous drug molecules to manipulate the PK and PD, thus enhancing their therapeutic efficiency and mitigating the unwanted effects and demonstrating the potential of nanotechnology-based advanced drug delivery systems in the optimization of drug delivery. Nevertheless, owing to the significant influence of the NP attributes such as design, shape, size, and surface charge/morphology, presently more emphasis is given on the generation of NPs with robust features to enhance a better effect of these particles on the body and consequently yielding an advanced formulation with improved therapeutic performance, reduced toxicity, and improved patient compliance. The present trend of designing so-called smart NPs is expected to continue in the upcoming future as well.

Conflict of interest

The authors report no conflict of interest.

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