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REVIEW

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Pharmacokinetics of nanoparticles: current knowledge, future directions and its implications in drug delivery

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Abstract

Background Nanoparticles have emerged as a viable biological candidate with the possibility to be employed as drug carriers. They acquire high surface-to-volume ratios and unique physicochemical features such as biochemical, magnetic, optical, and electrical changes at the cellular, atomic, and molecular levels. This phenomenon has proven extensive utility for biomedical applications, as their biological activity has fewer adverse effects than traditional medications.

Main body of the abstract The new spectrum of nanomaterials—nanomedicines—has accomplished disease management by detecting, restoring, and regeneration of damaged tissues. Therefore, designing appropriate nanomaterial-based drug delivery systems for final clinical evaluations requires accurate knowledge of pharmacokinetic factors relevant to the LADME in order to meet the required criteria (liberation, adsorption, distribution, metabolism, and elimination). To identify and predict the in vivo reaction of nanoparticles, a deeper understanding of the link between the physicochemical properties of nanomaterials and their contact with the body is necessary. This will allow a distinguished comparison of traditional medicines and nanoparticles.

Short conclusion This review paper attempts to analyze the basic pharmacokinetic potential of nanoparticles in depth. Therefore, profiling the pharmacokinetic analysis will enable us to review the treatment outcome to overcome their adverse properties, provide a broad overview, and deliver remarkable ways to advance the use of nanoparticles in the biomedical industry.

Keywords Nanoparticles, Drug carriers, Pharmacokinetics, Biomedical applications

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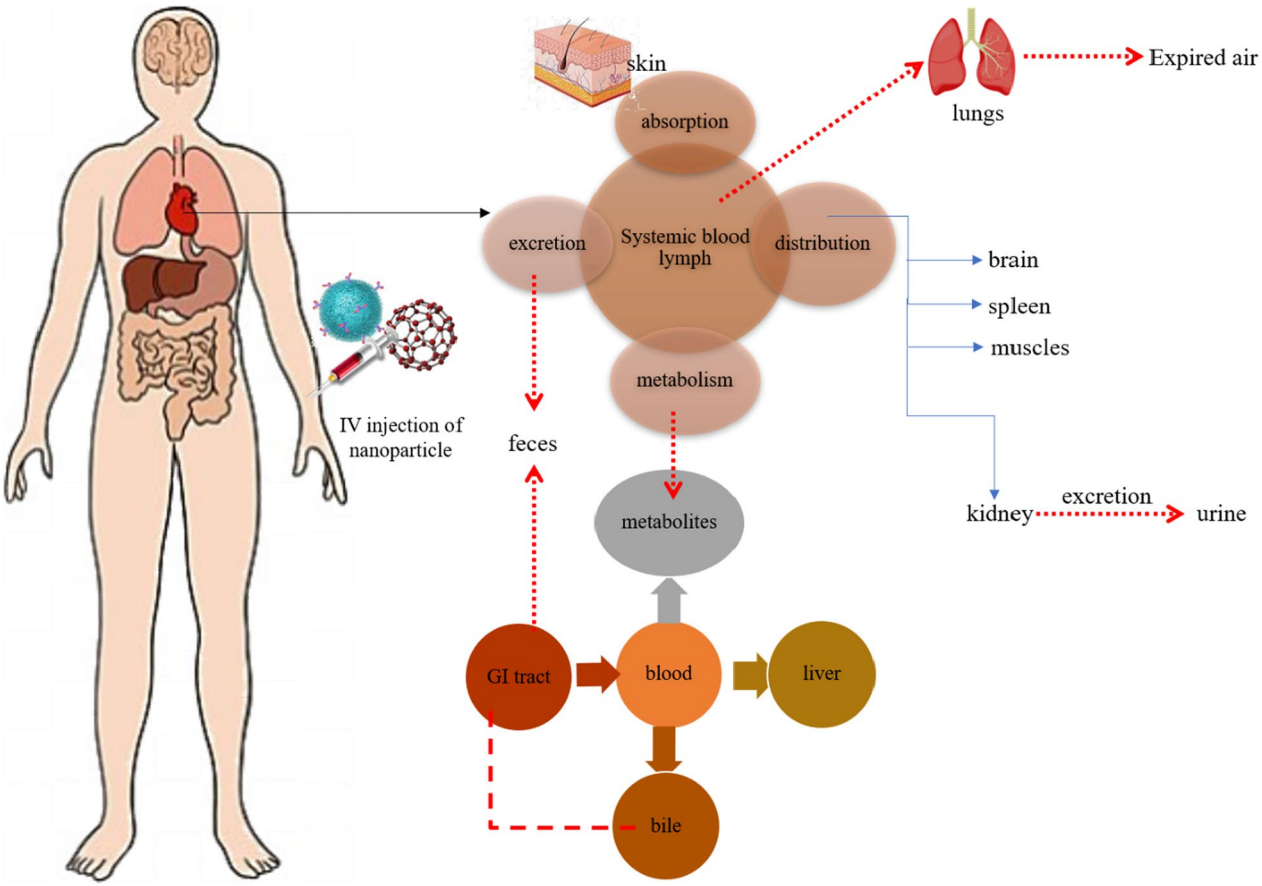
Graphical abstract



Background

The progression in science and technology has delivered toward the synthesis and development of nanoparticles. The scientific community has also embraced relatively inexpensive, safe, and cleaner products and technology compared to conventional strategies. Since nanotechnology has the capacity to be applied to many facets of life, it offers a solution to every existing issues [1]. Recent advancements have revealed their dual capabilities, such as diagnosis and treatment for a disease, with a steadily growing interest in the field of nanosystems to implement them in several biomedical applications [2, 3]. Also, the concept of nanopharmaceuticals has been employed by adding additional functionalities to the existing active compounds [2]. With these capabilities, nanotechnology has aided the hunt for materials at the molecular level by assessing compounds with exceptional qualities for biomedical applications (Fig. 1).

In recent decades, nanoparticles have become the go-to delivery system for pharmaceuticals and diagnostic reporters. When attempts were made to create dimeric, trimeric, and hexameric RNA nanoparticles by allowing several re-engineered natural RNA molecules to self-assemble, the first supporting evidence was reported in 1998 [4, 5] that improved the activity cost-effectively by lowering side effects and dosage. Therefore, they can be a better drug delivery platform by improving solubility and allow faster administration with excellent pharmacokinetic profiling. This will aid in targeting specific diseased tissues or cells to provide selective delivery, by providing manifold actions with a single particle [5].

Numerous biological applications have used these nanoparticles, such as targeted drug delivery, magnetic hyperthermia, contrast agents for MRI and CT, light ablation therapy, and biosensors [6]. Table 1 lists the biomedical applications of different nanoparticles. These nanoparticles are an interesting choice for use in the diagnosis, treatment, and regeneration of biological

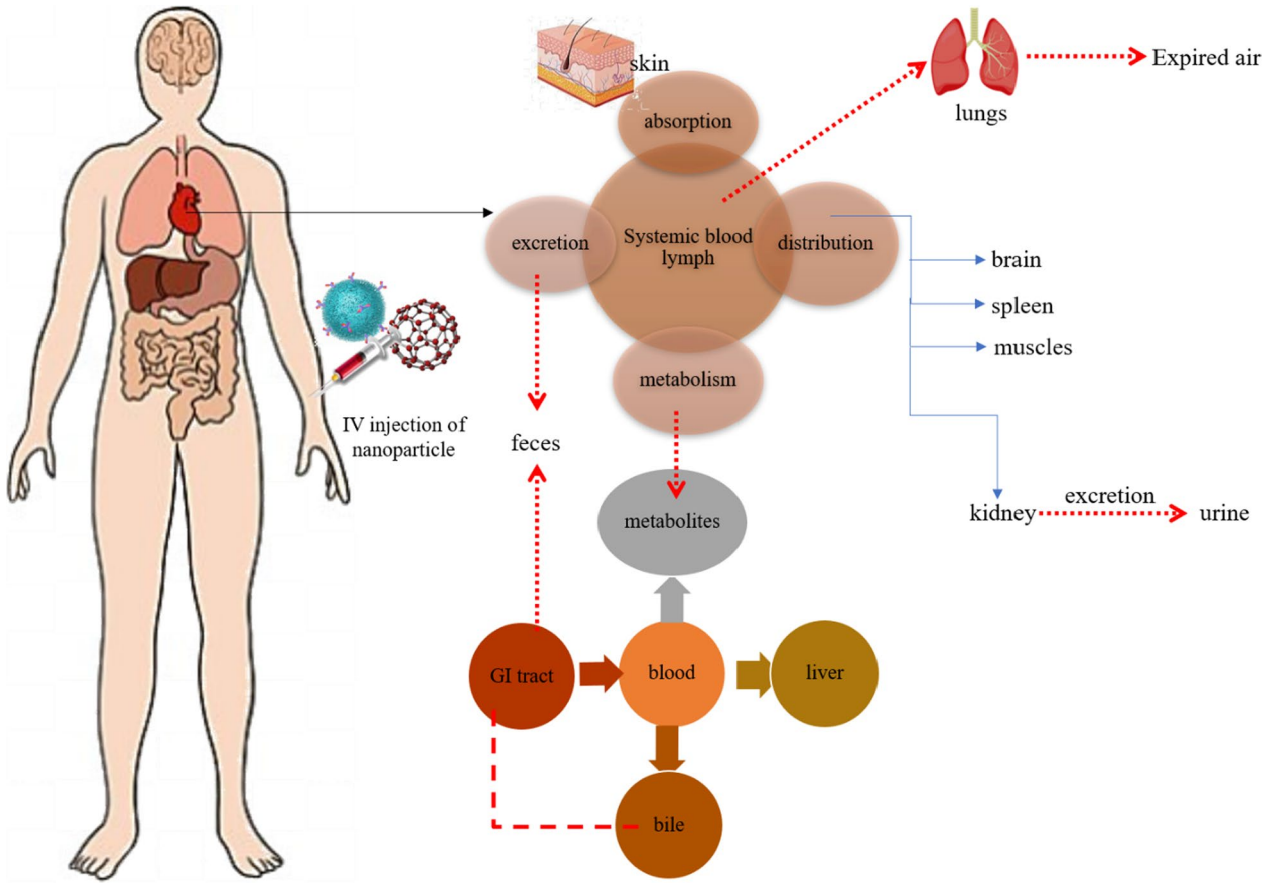


Fig. 1 Overall ADME mechanism and fate of nanoparticles

Table 1 Biomedical applications of various nanoparticles [7]

Metallic nanoparticles		Non-metallic nanoparticles	
Name	**Applications**	**Name**	**Applications**
Iron-oxide nanoparticles	MRI Contrast agents, treatment for hyperthermia, drug delivery, gene delivery, bioimaging	Carbon nanoparticles and Carbon nanotubes	Drug delivery, bioimaging, tissue engineering, and biosensing
Gold nanoparticles	Bio-imaging, photothermal therapy, drug delivery	Calcium phosphate nanoparticles	Prosthetics and scaffolds in tissue engineering application
Silver nanoparticles	Drug delivery, wound dressing, antimicrobial agents, cancer therapy	Biodegradable dextran nanoparticles	Micelles in nano-drug delivery
Zinc Oxide Nanoparticles	Paint and cosmetic industry, antimicrobial and anti-cancer application	Gelatin	Scaffolds in tissue engineering, biosensing, drug and gene delivery
Titanium oxide nanoparticle	Cancer therapy, anti-bacterial application in dentistry, Bone and dental implants	Chitosan nanoparticles	Diabetes treatment
		Polymeric nanoparticles	Cancer Therapy

systems due to their capacity to change their properties in a systematic manner by controlling their structures and characteristics at the nanoscale [7]. A wide range of materials and methods have been used to create nanoparticles for biological applications; as a result, their sizes, morphologies, and physicochemical characteristics are very diverse. Also, surface ligands are routinely applied to inorganic cores to provide colloidal stability

and functional groups for a specific protein or biomolecule the nanoparticles target.

Here, pharmacokinetics is a crucial component of drug delivery research through the design of suitable human clinical studies. Therefore, it is important to comprehend the ADME properties of pharmacological candidates to comprehend the pharmacokinetic and metabolic characteristics of therapeutic molecules [8]. To produce nanoparticles with an average particle size and the best drug entrapment efficacy, the formulation factors must be further improved since they might also have an impact on the preparation. These parameters should be compared to formulation variables such as stabilizing agent concentration, drug concentration, and nanoparticle concentration [9]. Specific factors, including physicochemical properties, permeability, and efflux movement, will be assessed in relation to absorption. Using the acquired information, in vivo models can be used to evaluate the overall amount of drug absorbed in the gastrointestinal tract. The degree of drug dispersion can then be determined using transporter assays, tissue-to-plasma partition coefficient, and the blood-to-plasma partitioning ratio. Furthermore, metabolic rates and clearance pathways in metabolism can be identified using hepatic and extrahepatic enzyme studies. Apart from this, information on drug excretion and elimination is also provided by metabolic, biliary, and renal clearance. Also, in vitro-in vivo extrapolation (IVIVE) has been used frequently to assess these parameters to estimate human pharmacokinetics [9]. By assessing all these parameters, the safety of nanoparticles comes into play [10]. In order to validate various nanoparticles for use in real-world biomedical applications, their pharmacokinetic properties should be examined. The pharmacokinetic properties of nanoparticles employed in numerous biomedical applications are listed in this review paper.

Physiology-Based pharmacokinetic modeling (PBPK) of nanoparticles

Biokinetics is the evaluation of absorption, biodistribution, xenobiotics, and toxicity variables in relation to external exposure, internal dose, and the probability of adverse health effects. The capacity of a pharmacokinetic model to predict is contingent upon the appropriate choice and formulation of the mathematical functions that parameterize the crucial elements controlling the kinetic process. Mathematical models simulating the rate processes of drug absorption, distribution, and elimination can be developed to characterize and forecast drug concentrations in the body as a function of time. In order to achieve the ultimate goal of the treatment regimen, the field is always evolving to keep up with new and innovative drug delivery methods and therapeutic approaches [11].

To comprehend this, physiologically-based pharmacokinetic (PBPK) models have been shown to predict such relationships accurately. A PBPK model is a powerful tool for calculating the accumulation time course of chemicals in organisms and target tissues. It can be used in a quantitative risk assessment framework. This modeling supports understanding and predicting the deposition of the target component within organs and tissues in a time-dependent manner [12]. The organization of the circulatory system, organ and tissue volumes, tissue partition coefficients, and tissue blood flow, among other anatomical and physiological parameters, can be evaluated in this study. These models aid in the description and prediction of the time-dependent targets of interest deposited inside organs and tissues [13].

However, biokinetic properties are anticipated to differ dramatically in the case of nanoparticles. Consequently, when creating nanoparticle-based PBPK models, novel factors must be taken into account. While the exchange of small molecules between blood and tissue is often flow-limited, the flow of nanoparticles between blood and tissue is typically diffusion-limited. Depending on their size, shape, charge, coating, and aggregation state, the nanoparticles that have been put into the bloodstream have been promptly taken up by phagocytic cells in organs like the liver and spleen [14].

PBPK models offer quantitative data on ADME kinetic processes by incorporating the physiological traits of animals and the physiochemical characteristics of toxicants. The dynamic interactions of nanoparticles in living organisms, such as the transit kinetics over bio barriers, have been modeled using a PBPK model based on metal nanoparticles. They have successfully guided experimental design, evaluated hypotheses, and conducted research on mechanical processes. As a bonus, they have decreased the cost-effectiveness of animal testing. This model will eventually be able to simulate and forecast the biodistribution and response of human nanoparticles [15].

As a practical technique for gaining mechanistic knowledge of the important components and sources of PK variability and for predicting drug exposure in therapeutically relevant conditions, PBPK modeling has come into its own. When combined with pharmacodynamic (PD) models, which connect exposure to target tissues to pharmacological effects, PBPK modeling can forecast efficacy and toxicity. Carbon nanoparticles, polymeric nanoparticles, nanocrystals, silver nanoparticles, liposomes, gold-dendrimer composite nanoparticles, and other nanoparticles have all been studied using PBPK

models. The development of a PBPK model is mentioned in Fig. 2.

Here, the tissues from the body are used as building blocks or compartments to develop PBPK models. The body tissues include the brain, intestines, heart, kidney, liver, lung, spleen, muscle, and fat tissues. If the body's remaining tissues are not from the target organ, certain tissues may be disregarded if they are not necessary for mass balance. Usually, these tissues are grouped into a carcass or remnant compartment. Tissues with similar kinetics may also be grouped together to make the model easier to understand. The circulatory blood system and, in some circumstances, the lymphatic system connect all tissue compartments in PBPK models, just like in physiological systems [16, 17].

The difficulty in using nanoparticles for medicinal purposes is caused by the lack of a good pharmacokinetic model to describe the nanoparticles' tissue distribution mechanism. For more effective therapies with fewer side effects, pharmacokinetic statistics have frequently been utilized to predict the quantity and dosage schedule required. For instance, the blood content of anticancer medications is highly correlated with both their efficacy and toxicity. However, the PK profile of blood cannot reveal how anticancer medications conjugated with nanoparticles are distributed throughout the body's tissues [18]. When employing nanoparticles to deliver anticancer medications, tissue selectivity can be improved due to the selective uptake of nanoparticles in particular tissues. Numerous anticancer medications that are injected into tissues that are not their intended targets may have negative side effects. However, a high concentration of anticancer drugs accumulating in the target tissue usually yields a greater therapeutic benefit. In order to understand how the body reacts to anticancer medications in nanoparticles and how nanoparticles affect the efficacy of anticancer agents, it is essential to create a pharmacokinetic model to represent the tissue distribution process of any drugs conjugated with nanoparticles [18, 19].

Factors affecting the utility of nanoparticles in biomedicine

The pharmacokinetic characteristics of small-molecule drug compounds and those in nano-formulations are vastly different. These discrepancies in pharmacokinetics may be attributable to the fact that the nanoparticle distribution in the body outnumbers the small molecule compounds present in the system. Consequently, evaluating the pharmacokinetic properties of nanoparticles will allow them to break out of the existing and established

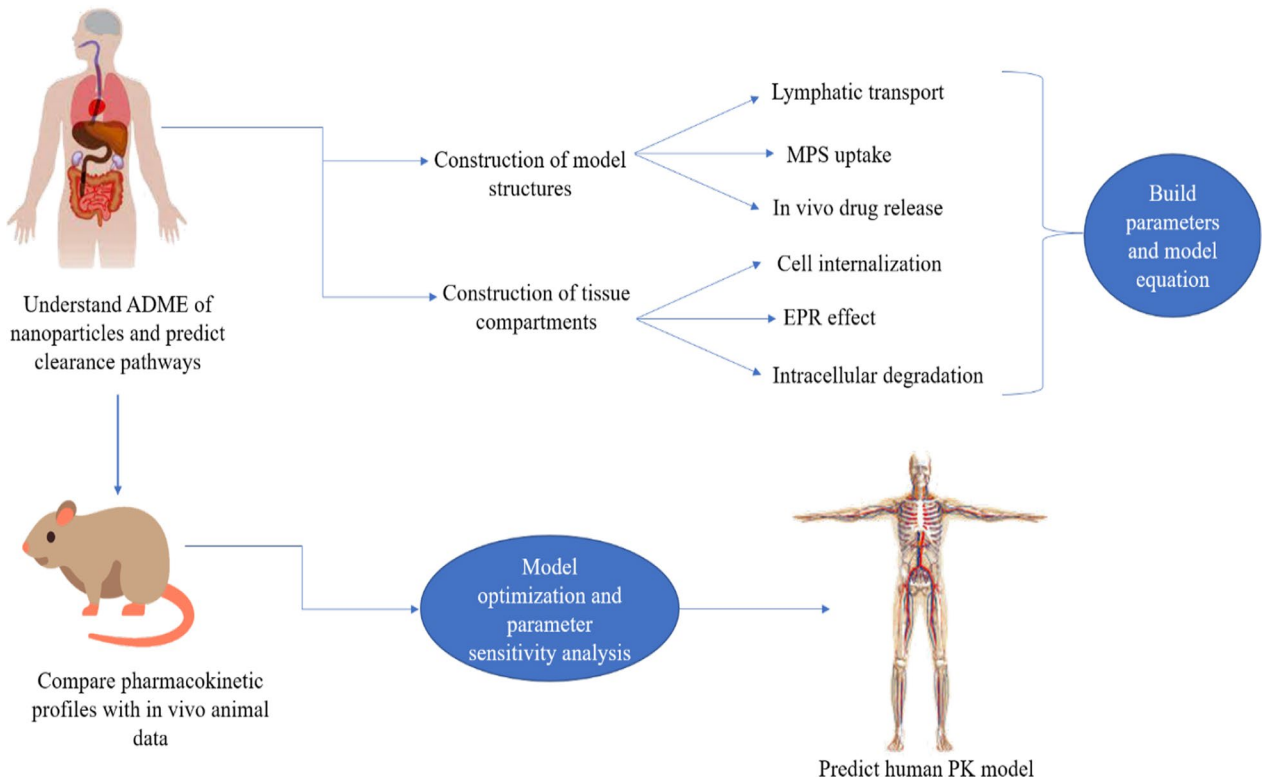


Fig. 2 Developmental process of physiology-based pharmacokinetic modeling (PBPK)

framework, allowing for the investigation of new pharmacokinetic characteristics [20].

Most nano-formulations can be categorized as hard or soft-type based on their physical characteristics, referring to their exterior flexibility. Effective pharmacokinetic differences are considered to result from differences in the exterior flexibility of the nano-formulation, as they might act differently in the body. Therefore, future findings on in vivo pharmacokinetics between these two categories must be conducted. A list of hard and soft nano-formulations is listed in Fig. 3.

To kick-start this work, recent studies have used population pharmacokinetic analysis to compare methotrexate-loaded nanoparticles and nanoemulsions as hard-type and soft-type nanoformulations. A foundation model that could explain the pharmacokinetics of free methotrexate solution and methotrexate-loaded nano-formulations was first created. In comparison to free methotrexate solution, methotrexate-loaded nano-formulations showed significantly higher bioavailability and lower clearance values. This was confirmed by analyses using both non-compartmental analysis and population pharmacokinetic models. The enhanced bioavailability and lower clearance values of nanoemulsions relative to nanoparticles were also evaluated using the same procedures used to evaluate free methotrexate

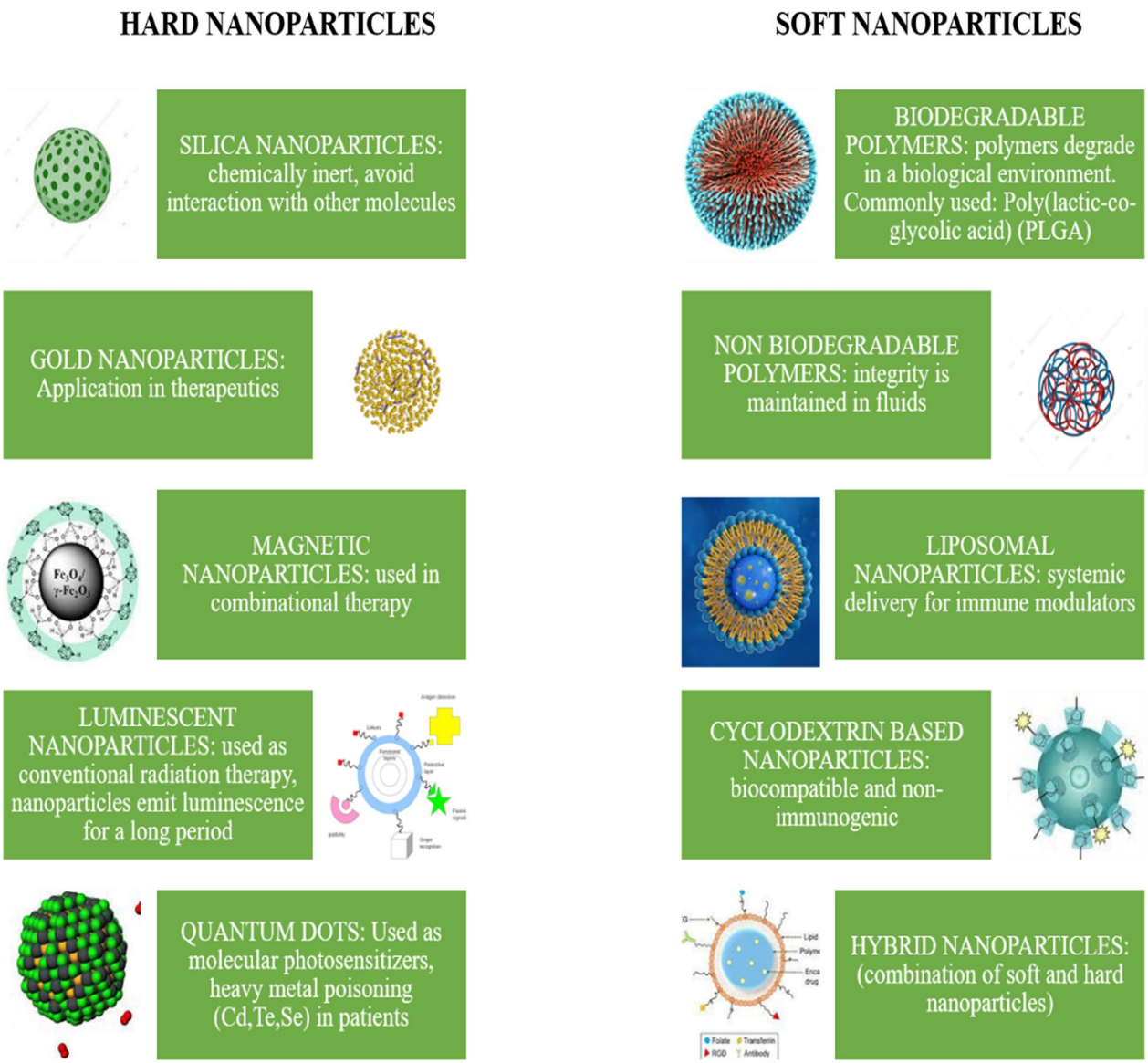


Fig. 3 List of potential Hard and Soft nanoparticles used in biomedical applications

solution and methotrexate-loaded nano-formulations [19].

Also, the complexity of nanoparticles makes the disposition of drugs difficult. Additionally, numerous particle properties, including composition, size, shape, charge, surface chemistry, and particle interaction, influence every feature in the biological system. All of these parameters have been influenced by the physiological environment. Rather than beginning from scratch, improving the characteristics of nanoparticles can be achieved by adhering to the norms of metabolism. By doing so, the goals of medicine can be achieved by satisfying the requirements of physiological conditions [4].

Size

Size is regarded as one of the most critical aspects of drug loading and other treatment characteristics. It has a considerable effect on nanoparticle clearance and dispersion. The nanocarrier's incapacity to get through the cell membrane is also largely due to its size. The absorption of macromolecules, proteins, and peptides in the gastrointestinal system and their transport to the intended site are solely dependent on the surface functionalization of nanoparticles. Thus, pore size remains a major barrier to future progress in nanomedicine, especially for biological applications [20]. On the basis of the Enhanced Permeability and Retention (EPR) effect, the biophysical characteristics of the particle and its ability to target tumors affect the blood circulation time of applied nanoparticles [21].

When removed too fast, nanoparticles in lesions may lose some of their ability to aggregate. However, prolonged retention within the body may contribute to increased toxicity. Recent research has indicated that nanoparticles smaller than 600 nm in size can be utilized due to the EPR effect. However, particles smaller than 6 nm will be eliminated by the kidneys. Also, the half-life of nanoparticles increases as their size range grows from 10 to 100 nm. Therefore, optical particle sizes should be chosen with nanoparticle and biological organ size interactions in mind. In order to create a balance between targeting and clearance, it is also required to exclude hazardous properties. Additionally, pH, charge, and hydrophilicity can affect particle size [18]. Figure 4 explains the potential role of size of nanoparticles impacting the system.

The surface area to volume ratio of small particles increases. This would suggest that more drug is present on the particle's surface than on the surface of a bigger molecule. A faster rate of drug release would result from being close or at the surface. Large surface area to volume ratio nanoparticle systems would be advantageous, but toxicity must always be regulated. The biological fate of a nanoparticle is determined by its size, as they are filtered and eliminated by the vascular and lymph systems [21]. It has been emphasized that particles 200 nm or larger have

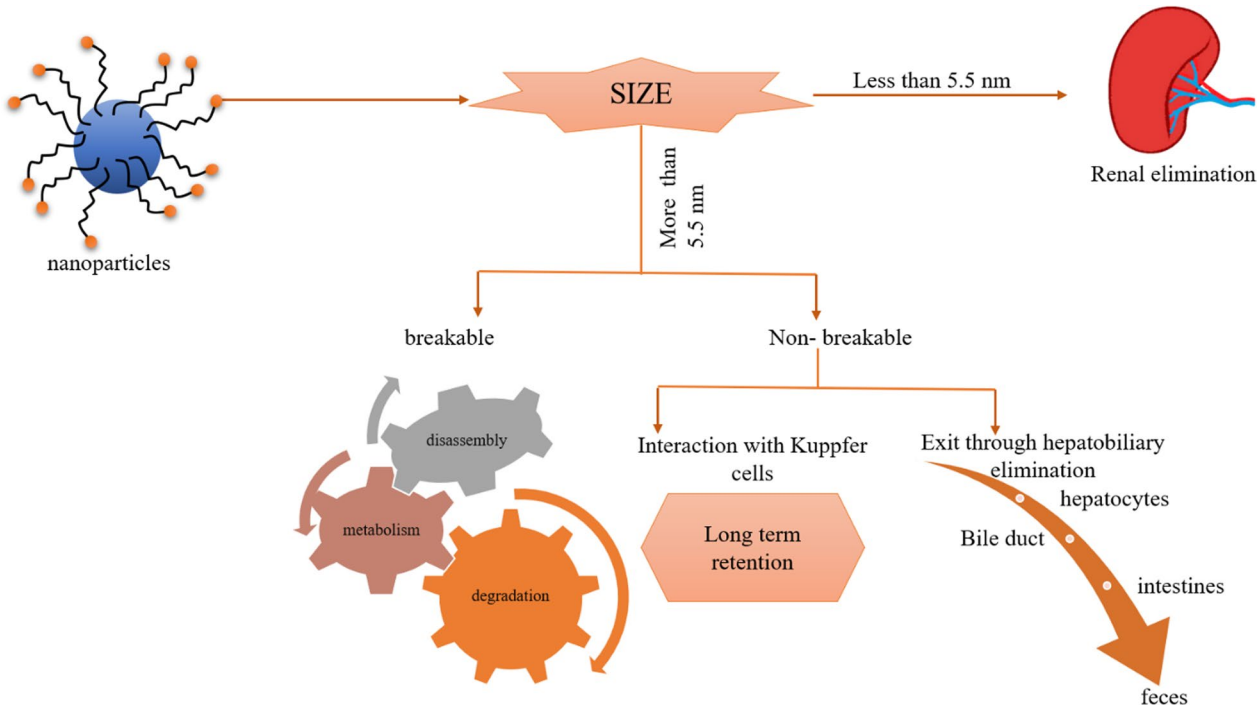


Fig. 4 Role of size as a checkpoint at the entry of nanoparticles in the human body

been found to have a tendency to activate the lymphatic system and leave the body more quickly. Accordingly, it appears from the analysis of the available literature and the discussion thus far that a nanoparticle's ideal size is around 100 nm. Due to the particle's small size and high surface area to volume ratio, it might cross the blood–brain barrier (BBB) without being immediately cleared by the lymphatic system [22].

The biodistribution of long-circulating nanoparticles for achieving therapeutic efficacy is significantly influenced by particle size and surface composition. It has been observed that these parameters interplay with physiological properties such as hepatic filtration, tissue extravasation, tissue diffusion, and kidney excretion [23]. The size of the nanoparticles has a significant impact on how well proteins are absorbed. When serum protein was added to pegylated polyhexadecylcyanoacrylate (PHDCA) nanoparticles of different sizes, medium (100–200 nm), and large (> 200 nm) for two hours, a significant association between particle size and protein uptake was seen. Examined and contrasted with that of larger nanoparticles of the same formulation was the protein absorption of small nanoparticles (80 nm). The effect of protein absorption on nanoparticles of various sizes was shown through analysis of nanoparticle uptake by murine macrophages and blood clearance kinetics. Smaller nanoparticle formulations were found to empty the blood twice as slowly as bigger nanoparticle formulations [24, 25].

Regarding particle size distribution, the "polydispersity index" is used to characterize the size range of lipidic nanocarrier systems (PDI). Two critical metrics for assessing a drug-loaded nanoparticle formulation are particle size and PDI, which are dependent on a variety of variables including composition, sonication duration, and extrusion temperature. Using the iterative trial and error methodology, empirical approaches are commonly employed to adjust these independent parameters in order to get a minimum particle size with a narrow size distribution. This index has no dimensions and is scaled, so values less than 0.05 are often observed with extremely monodisperse standards [25, 26]. Table 2 lists the effects of nanoparticle administration dependent on particle size.

Shape

As vital as size is for prolonged medication delivery, nanoparticle shape is also crucial. Spherical nanoparticles are a viable alternative for drug delivery, but anisotropic shapes, like dendrimers, may be the best choice due to their significant surface area. Such structures may effectively seat and bind the drug, which is advantageous for prolonged drug administration [30].

Several factors contribute to the influence of particle form since certain organs in the body appear to favor particles with particular shapes. For instance, nanoparticles with an irregular form prefer to collect in the spleen, whereas particles with a rod-like structure prefer to collect in the lungs. Nonetheless, the precise mechanism underlying this predilection remains uncertain [31]. Interestingly, shape-specific nanoparticles, such as spherical, cubic, rod- or worm-shaped ones, will affect cellular uptake. Spherical particles demonstrated the largest uptake in terms of weight when compared to cubic, spherical, and rod-like gold nanoparticles, but rod-like nanoparticles demonstrated the highest uptake in terms of quantity. Similar results were obtained with DOX-loaded polymeric nanoparticles, with rod- and worm-shaped nanoparticles being more readily absorbed by MCF-7 cells than spherical nanoparticles [32, 33].

A crucial step in the intracellular delivery of drugs is through the cellular absorption of nanoparticles. After being administered in vivo, nanoparticles interact with

Table 2 Impact of delivery of nanoparticle-based on the size factor [27–29]

Ideal particle size	Treatment	Impact	Barriers
100–150 nm	Systemic drug delivery	Targeted deposition, bioadhesion, reduced dosage frequency, and sustained release	Size of 20–100 nm might leave the bloodstream via leaky capillaries and renal filtration that cannot be absorbed
1–5 µm MMAD (Mass median aerodynamic diameter)	Pulmonary drug delivery	Biocompatible, targeted delivery, produced in diverse size ranges	Size distribution is of primary concern- it influences the effectiveness of the drug
150–200 nm	Drug delivery to tumors	Therapeutic nanoliposomes have been used- reported to produce good efficiency in targeting tumors	Mononuclear Phagocyte System (MPS) uptake and Enhanced Permeation and Retention (EPR) effect
100–300 nm	Transdermal drug delivery	Lipid-based encapsulate on the system are preferable as they enhance the mode of action (edge activators)	Yet to find full potential and find an alternative to oral medicines and hypodermic injections
93–96 nm	Drug delivery to the brain	Dual targeting strategy with higher therapeutic efficiency and potential drug delivery	Constraints due to blood–brain barrier (BBB)

various types of cells depending on the target region. The critical role of particle shape on cellular uptake, kinetics and mechanism, intracellular distribution, and cytotoxicity of nanoparticles has been acknowledged. Critical studies in this area have been motivated by the apparent influence of particle shape on cellular internalization of nanoparticles employing a variety of cells, including macrophage, epithelial, endothelial, and immune cells [34].

The performance of nanoparticles in terms of blood circulation time, cellular internalization, bio-distribution, endocytosis by immune cells, and residency duration within the cell have all recently been shown to be greatly impacted by the shape of the particles. For instance, non-spherical particles have been found to circulate more slowly, undergo less macrophage phagocytosis, and be taken up by cells less readily than their spherical counterparts [35].

The influence of particle shape was investigated on how microscopically small polystyrene particles interacted with macrophages. Ingestible particles were exhibited, and they created a dimensionless shape-dependent parameter related to the normalized length curvature (Ω). Only when the particle volume was bigger than that of the macrophages did particle size or volume change completely when the particle gets internalized during phagocytosis [36].

The biodistribution of nanoparticles was significantly impacted by particle shape as well. After being administered orally and intravenously to healthy lab animals, the biodistribution of nanoparticles with various geometries, such as rods, cylinders, quasi-hemispherical particles, and many more, was examined and contrasted with that of spheres. Variable organs contained variable concentrations of nanoparticles depending on the form of the particles. For instance, in a comparison of the biodistribution of four different shaped particles (discoidal, quasi-hemispherical, cylindrical, and spherical), it was discovered that the concentration of discoidal particles in the liver was the lowest of all the shapes examined, while their concentration in the other organs was higher than that of any of the other shapes [36].

According to one theory, the propensity of discoidal particles to float toward vessel walls was what caused them to accumulate in other organs and escape from phagocytosis to cause the lowest discoidal particle concentration in the liver. In the same study, spherical silica nanoparticles showed significant RES absorption while cylindrical particles mostly aggregated in the liver. In a different study, when coated with ICAM antibodies, both rod-shaped and spherical particles demonstrated enhanced lung targeting in mice after 30 min. Additionally, when coated with IgG antibodies, both rod-shaped and spherical particles displayed improved liver and spleen uptake [37].

Surface chemistry

Particle solubility, aggregation qualities, ability to cross biological barriers, biocompatibility, and targeting properties are all influenced by surface properties. In order to interact favorably with the aqueous environment of biological systems, the majority of nanoparticles utilized as drug delivery devices have hydrophilic surfaces. Some nanoparticles are routinely given a surface charge to increase their stability and prevent further particle aggregation in aqueous solutions via electrostatic repulsion. However, the appropriate surface charges and charge densities aid in extending blood circulation duration and reducing the dissemination of nonspecific, unwanted nanoparticles. These variations may be attributed to the nature of charged groups, changes in nanoparticle stability, and other confounding variables such as non-uniform particle sizes [38, 39].

When compared to neutral particles of the same size, cationic or anionic particles are more stable and capable of avoiding non-specific cellular absorption by phagocytes. Because of their intense interaction with negatively charged genetic material and their capacity to adhere to cell surfaces, cationic nanoparticles have enormous potential as medication delivery vehicles. Through endocytosis, they enable loading of genetic materials that cannot pass through cell membranes and guarantee efficient cell uptake [40].

Functional groups can be conjugated to alter the surface charge of nanoparticles. Positively charged nanoparticles are readily drawn to the cellular membrane due to its negative electrical charge and are mostly ingested via endocytosis pathways. Although it was predicted that negatively charged nanoparticles would be taken up far less than neutral ones, multiple reports have found the opposite to be true. For instance, research with carboxy methyl substituted dextran-coated NPs incubated with Caco-2 human colon cancer cells and having a surface charge between 50 and + 5 mV suggests internalization despite increased negative charge. The majority of negatively charged nanoparticles were found to have non-specific internalization routes using inhibitor tests [18].

The surface charge and the kind of functional groups on nanoparticles also have an impact on the density and type of proteins that are adsorbed. It has been demonstrated that cationic nanoparticles bind to plasma proteins with isoelectric points less than 5 while anionic nanoparticles bind to proteins with isoelectric points more than 5 using polystyrene nanoparticles modified with either basic or acidic functional groups (Sabourian et al. 2020). Additionally, the surface charge density of

nanoparticles affects how proteins bind to their surfaces. IgG and albumin, for example, both favor binding to nanoparticles that have strongly basic (NH_2) or mildly acidic (COOH) groups. Its adherence to the surface of nanoparticles affects the in vivo cellular destiny of nanoparticles because IgG, among other proteins, affects particle clearance from the circulation [18].

The clearance of nanosystems needs to be taken care of first. Nanoparticles are susceptible to the immune system's natural defense against foreign substances because the lymphatic system can identify them. Because blood components bind to hydrophobic nanoparticles more strongly, they are more likely to be removed from the body. It would make sense to believe that turning the surface of hydrophobic nanoparticles hydrophilic will lengthen their stay in circulation because they are easily removed [41].

Polyethylene Glycol (PEG), a hydrophilic and generally inert polymer, prevents plasma proteins from adhering to nanoparticle surfaces (opsonization), effectively eliminating significant dosage loss. PEGylated nanoparticles are frequently referred to as "stealth" nanoparticles because, in the absence of opsonization, the reticuloendothelial system (RES) cannot detect them. Clearance problems have been solved by building polymer complexes, although small particle aggregation remains a problem due to their high surface area especially with nanoparticles like dendrimers, quantum dots, and micelles [42].

Biological barriers

Effective biodistribution and drug delivery are challenging to achieve even under physiologically normal circumstances because administered nanoparticles encounter physical and biological barriers such as shear forces, protein adsorption, and rapid clearance that restrict the amount of nanoparticles that reach the intended therapeutic site. With a broad, one-size-fits-all strategy, these hurdles can be even more challenging to overcome as disease conditions frequently alter them. These alterations in biological barriers can occur at the systemic, microenvironmental, and cellular levels and vary not just among diseases but also from patient to patient, making them challenging to separate and broadly characterize [43].

The human body has many biological defenses against outside invaders, wherein the immune system's cellular and humoral components act as mucosal barriers. Nanoparticles must thus overcome a number of obstacles in order to achieve their objective. Due to their special size and capacity to surface-functionalize to include the required characteristics, they are well-suited to get around these restrictions. Here, excretion, blood flow, corona, and phagocytic cells can all have an adverse effect on the stability and distribution of nanoparticles when they are in circulation. The physiochemical features of the nanoparticle platform determine the precise effects of each of these environmental elements, which has led to broad design concepts intended to modify these qualities to produce desirable results [16].

The concept of passively directing nanoparticles to tumors was inspired by the EPR effect. Angiogenesis occurs in defective hypervasculature and insufficient lymphatic drainage during tumor formation. By extravasating through fenestrated blood arteries, nanoparticles can accumulate long-circulating macromolecules more effectively and show various viable options for the site-specific localization of chemotherapeutics [44]. Long-circulating drug delivery nanoparticles can bind to the therapeutic medication locally in the extracellular space, enter tumor tissues, and release it there [45]. Therefore, the only factors that affect the pharmacological action within the biological system are the targetability and stability of the nanoparticle delivery method. The obstacles that nanoparticles encounter when they enter the biological system are shown in Fig. 5.

The cellular membrane serves as a barrier to therapeutic medications and as a source of nutrition for the cells. The majority of therapeutic delivery using nanocarriers, including that of genetic components with intracellular activity, necessitates cell penetration. This is made possible by the more than 400 transporters that can be found on a cell's surface. Interactions with these transporters help nanoparticles enter the body [46].

Also, nanoparticles encounter variable flow rates in the bloodstream that cause shear stress, which could harm the platforms or their cargo and hinder extravasation. These fluid forces have the ability to remove the nanoparticle's surface coatings and stop them from concentrating on vessel walls and extravasating either transcellularly or paracellularly to reach target tissues. Circulating nanoparticles come into touch with blood-suspended biomolecules, cells, and vessel walls. A corona develops on the surface of nanoparticles due to the non-specific adhesion of serum proteins and lipids. The physicochemical properties of the nanoparticle surface, which control the adsorption or desorption of proteins from biological fluids, as well as the biomolecules present in blood, determine the corona's composition [47].

ADME profiling of nanoparticles

The pharmacokinetics (PK) and toxicokinetics (TK) of nanoparticles characterize their absorption, distribution, metabolism, and excretion (ADME). According to the primary research, nanoparticles do not conform with conventional dose measures. Despite the significant dose-related variability of nanoparticles in bulk, the majority of research has employed mass-based dosimetry

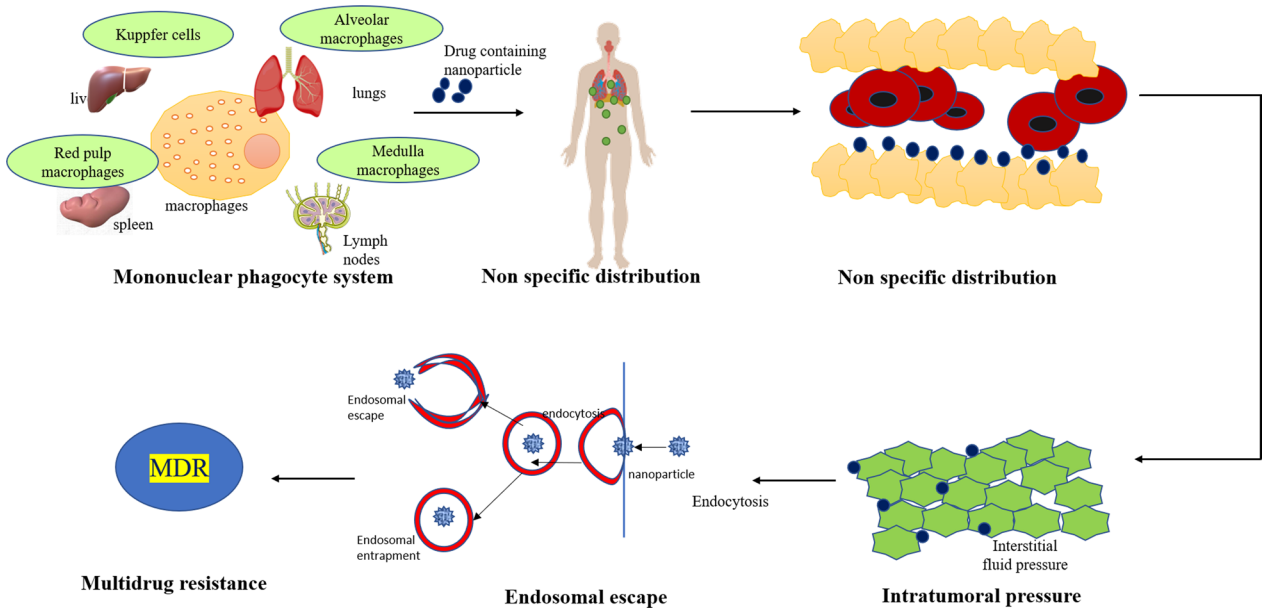


Fig. 5 Barriers present in the biological system that prevent the entry of nanoparticles

to define nanoparticles. Understanding the biodynamics of nanoparticles is vital for developing effective and safe nanoproducts through a comprehensive understanding of ADME profiling and integrated kinetics pertaining to nanoparticles [27].

Systems for delivering nanoparticles show enormous promise for treating a wide range of illnesses, particularly cancer. The characteristics of nanoparticles are essential for controlling the drug delivery effect. Various ways have been studied by researchers to optimize the structure of nanoparticles. Increasing the biocompatibility of nanoparticles is one tactic. This can be accomplished by tweaking the composition of conventional nanomaterials and altering their surface. Liposomes, for instance, are artificial membranes with bilayer structures resembling those of cell membranes that are extremely biocompatible due to their inherent biodegradability, non-toxicity, and lack of immunogenicity [48]. Increasing the effectiveness of nanoparticle targeting is another tactic. Nanoparticles can be coated with a variety of cell membrane types, including cancer, immune, and red blood cell membranes, to give them biological properties akin to those of the parent cells. As a result, the nanoparticles can actively target particular tissues or cells. Enhancing the pace at which drugs load onto nanoparticles is the third tactic. To boost the drug loading capacity of nanoparticles, a variety of carrier systems have been investigated, including inorganic carriers (like mesoporous silica nanoparticles), organic carriers (like polymers like PEG), and metal–organic framework (MOF) carriers. Regarding drug loading efficiency and toxicity, these carrier systems offer varying benefits and drawbacks [49].

Orally administered nanoparticles may meet systemic clearance mechanisms, including chemical/enzymatic breakdown and direct elimination, such as feces when supplied via extravasation pathways. The loaded Active Pharmaceutical Ingredient (API) may be released if the nanoparticles degrade during administration, and the released API will follow its disposal route. To date, the majority of nanoparticles have been examined and created for intravenous administration; hence, once they enter the systemic circulation, nanoparticles are concurrently dispersed and removed from specific organs and tissues [50]. Figure 6 depicts various nanoparticle exposure routes and their fate within the human body.

Absorption

Absorption describes the process by which drugs loaded on nanoparticles travel through multiple routes from the administration site to enter the bloodstream. Nanoparticles have been delivered mostly orally and intravenously, with intravenous injection allowing nanoparticles to enter the bloodstream without absorption. Nanoparticles smaller than 500 nm have a great capacity for circulation and stay in the blood, according to research. This improves the effectiveness of the attack on diseased tissues [51]. Nanoparticles move systemically with a pH shift from 3 to > 7 and include numerous intestinal enzymes capable of metabolizing the functional groups in an effort to be absorbed within the GI tract. Mucus,

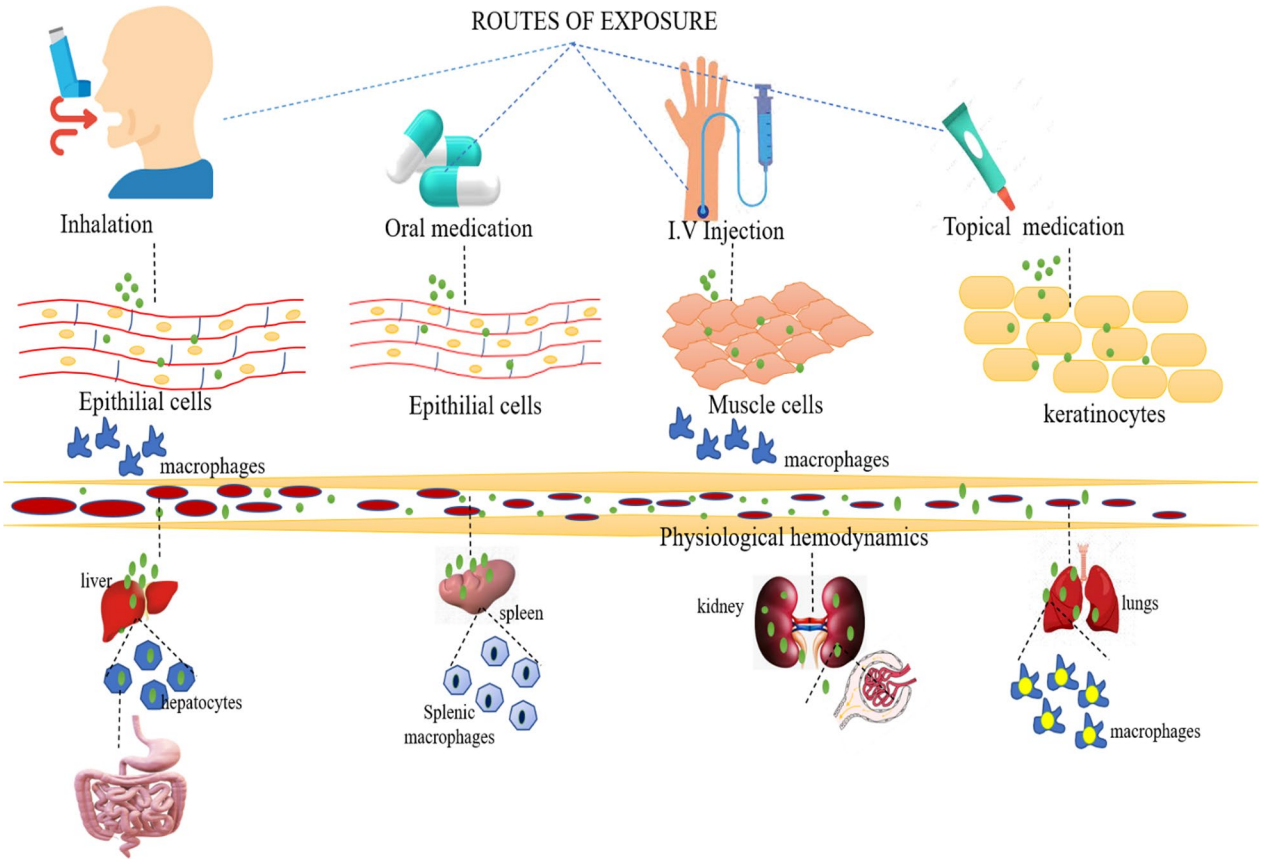


Fig. 6 Overall process of ADME in the human body

a heterogeneous anionic gel made up of lipid and glycoprotein polymers suspended in water, shields the lining of the digestive tract from toxins and promotes nutritional absorption [52].

Mammalian digestive systems are capable of processing food-related nanoparticle emissions makeup in a systematic way. Before splitting into atoms, it travels via the mouth, stomach, small intestine, and large intestine. Various models have been idealized to forecast how the human gastrointestinal tract will break down novel nanomaterials related to food. According to direct and indirect evidence, the integrity, aggregation, and surface features of food-relevant nanoparticles are primarily determined by the salt concentration, pH, and biochemicals in the luminal fluid matrix, determining their absorption into the systemic circulation [51].

To transport nanoparticles to the lungs, it is essential to comprehend their fate and how they interact with biological systems. In order to be effective, the inhalable medicine must overcome lung clearance (mucous hair escalation, alveoli), as well as the detoxifying activities of enzymes such as cytochrome P450. Nanoparticles offer benefits for systemic circulation and prolonged release into lung tissues, which reduces the need for frequent dosage and improves patient compliance. The thermal diffusion changes of air molecules interacting with the particles in the inspiratory and expiratory airflows are the main factors that control nanoparticle deposition in the airways [52, 53].

The intravenous method provides an almost immediate response and allows for extensive control over the dosage rate. It is also suitable for drugs that cannot be injected into muscles or other tissues or absorbed through the digestive system. It successfully handles the first-pass metabolism problem and exhibits effective administration of expensive intravenous drugs like peptides and proteins [17].

Regarding the interactions between nanoparticles and skin through the dermal pathway, recent research has shown that some nanoparticles can pass through the stratum corneum of the skin's outer layer while others can pass through deeper skin layers and enter the bloodstream. For a nanoparticle to penetrate the skin, it must possess specific characteristics; when dry nanoparticles are applied, variables including size, charge, zeta potential, and shape might change significantly. The evaluation

of moist skin surfaces can therefore be done using physiological solutions or synthetic sweat. Zeta potential and charges may be related to cell-nanoparticles interactions in culture, while their function in skin absorption is uncertain [17]. Based on the existing evidence, we may conclude that specific nanoparticles have shown skin penetration. The interactions between the various routes of exposure and the human body are detailed in Table 3

Distribution

The mechanism of transporting nanoparticles and their loaded therapeutics from circulation to tissues, intercellular fluid, and cells is referred to as distribution. Nanoparticles are disseminated throughout the tissues and other organisms via blood circulation after absorption. Here, many chemicals and nanoparticles attach to plasma proteins quickly and form a corona, with a reversible or irreversible complex that changes the surface characteristics of the protein [50]. Studies on biodistribution by Rowland et al. revealed that albumin and similar proteins might bind to nanoparticles functionalized with weak acidic and neutral ligands, whereas alpha-1-acid glycoprotein and related proteins bind to particles functionalized with essential ligands[52]. It is notable that, factors such as size, shape, and surface functionalization of the nanoparticles also influence the process of biodistribution within the system [53].

Since the nanoparticles are exposed to an environment that differs from their formulation buffers at an instant rate (temperature, pH, ion strength, composition, and shear stress), physical processes such as dilution in the blood and diffusion of nanoparticle composition, can reflect in altering the colloidal particle stability. Also, a reduced temperature distribution is observed when injecting nanoparticles into the bloodstream at higher loading levels. This causes specific nanoparticles to aggregate, swell, or dissolve. Additionally, nanoparticle components can be degraded chemically or enzymatically [54, 55].

Inside the system, multiple transport mechanisms, such as opsonization, protein corona formation, MPS uptake, EPR effect, target-mediated disposal, and lymphatic transport, are involved in the in vivo dispersion of nanoparticles [56]. Importantly, opsonization and protein corona formation can significantly impact nanoparticle biodistribution throughout the body. Especially, opsonization can obscure targeting ligands on the surface of nanoparticles, causing a substantial loss in nanoparticle selectivity to target cells and tissues, apart from enhancing nanoparticle removal via MPS absorption [15].

Once the nanoparticles enter the bloodstream, the protein packaging is the first barrier affecting the distribution of the nanoparticles. Opsonins easily recognize and remove large nanoparticles, thereby reducing their spread. In addition, the particle size of the nanoparticles increases after protein encapsulation, and the particle size also determines the physical penetration of the nanoparticles into different tissues. Because protein regulation and physical permeability play an essential role in the delivery of nanoparticles in vivo, the hydrophilicity and hydrophobicity of the nanoparticles can influence protein encapsulation. Thus, the distribution of nanoparticles can be controlled by varying their size and hydrophobicity, together with a smart nanoparticle design that improves their transmembrane capacity to achieve a rapid target delivery and response to disease treatment needs [57].

It has also been reported that nanoparticle transfer from blood circulation into the system is concentration-dependent, saturable and may not be subjective to a predetermined tissue partition coefficient. Passive diffusion dominates drug transport from blood vessels to tumors for small molecules, whereas convective transport-based EPR dominates the accumulation of non-targeting nanoparticles in tumors [58]. Figure 7 represents the biodistribution and interaction of nanoparticles in the human body.

Metabolism

There is a need to maintain normal energy balance inside the body when nanoparticle carriers are present. But in certain pathophysiological conditions, unsynchronized energy metabolism creates various problems, including muscle fatigue, apathy (when energy production is low), or thermogenesis (when energy production is high). Nanoparticles, along with or without conjugated particles, can be used to maintain energy balance

Table 3 Different routes of exposure of nanoparticles and their interaction with the human body [17]

Routes of administration	Interaction	Endpoint
Oral	Gastrointestinal tract	feces
Inhalation	Lung	Kidney (urine)
Intranasal	Nasal cavity	Metabolized in Kidney (urine)
Intravenous	Plasma circulation	Metabolized in Kidney (urine)
Intramuscular/subcutaneous	Peripheral compartment (tissues)	Kidney (urine)

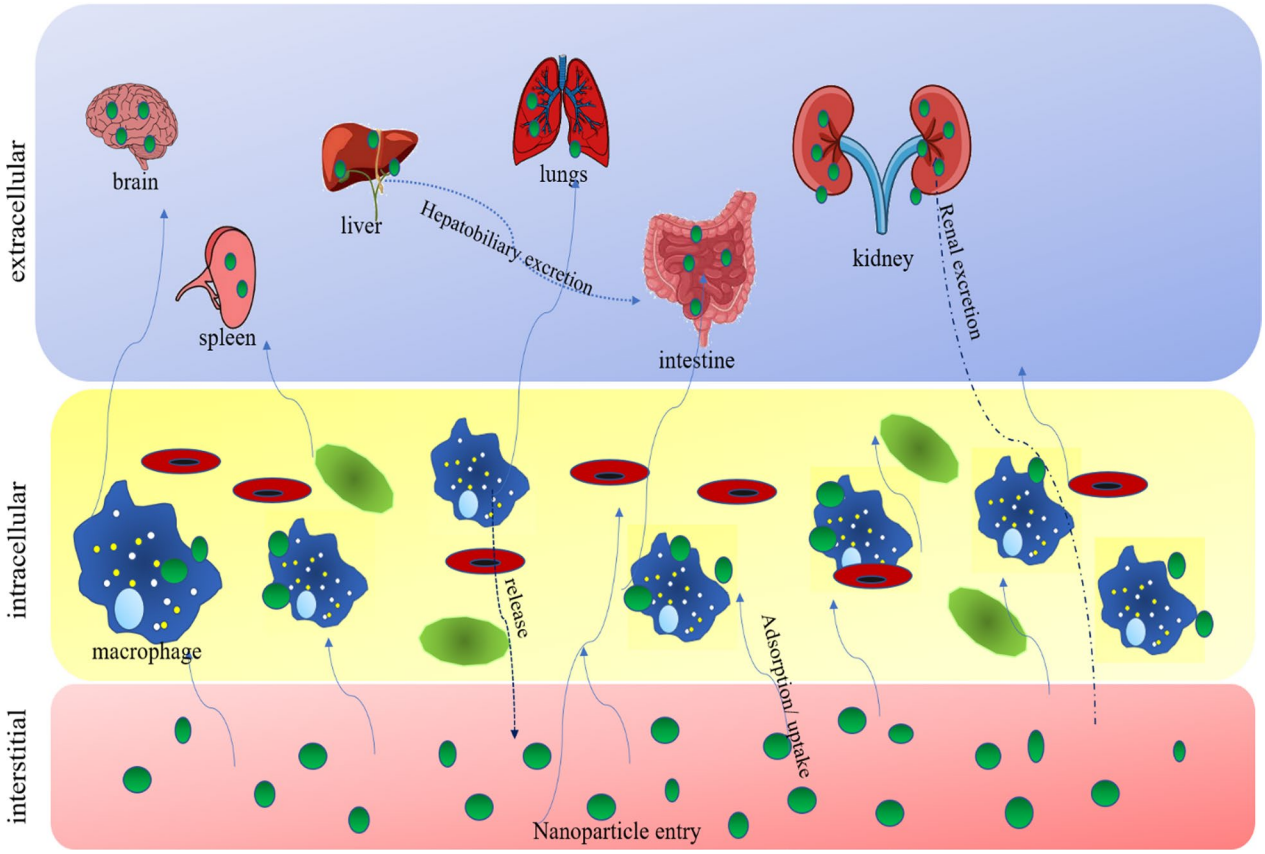


Fig. 7 Biodistribution and interaction of nanoparticles in the human body

inside the body. Recent trends in therapeutics indicated that nanoparticles are an integral part of future nanomedicines, but concern lies in studying the interaction of nanoparticles with living systems. When biologically active nanoparticles (whether beneficial or detrimental) enter the living system, mediate their effects, and depending on their size or surface chemistry, they can or cannot be eliminated from the body. So, the chronic effects and the fate of biologically active nanoparticles should be of immense importance while studying the therapeutic potential of nanoparticles [57].

The liver is the principal site of metabolism in this case. Hepatocytes, Kupffer cells, and hepatic macrophages are the functional components of the liver. Transporters, phase I and phase II metabolism enzymes, and biliary circulation are abundant in hepatocytes, allowing more significant lipophilic particles to be excreted. The GI tract epithelium and the liver are important extrahepatic location for chemical metabolism. Chemicals ingested by the intestine will travel through the first-pass metabolism of the liver. Because of their high perfusion rate, the lungs also contribute to metabolism. Also, to a certain extent, the kidney, skin, and placenta can also carry out xenobiotic-metabolizing processes [50].

In general, three distinct phases dictate the fate of ingested nanoparticles: the digestive phase, the absorption phase, and the circulatory uptake phase. Due to antral contraction, retropulsion, and stomach emptying, the digestive phase physically breaks down the nanoparticles into a coarse emulsion. Gastric lipase hydrolyzes the emulsion into more polar monoglycerides and fatty acids, which enter the metabolic process. Most orally administered nanoparticles or metabolites enter the systemic circulation via direct absorption that gets directed into the portal blood. Whereas, in the case of lipophilic medicines, the nanoparticles escape the lymphatic route avoiding hepatic first-pass metabolism. It has been noted that oral administration may have low bioavailability due to extensive metabolism [45].

Furthermore, the actions of the cytochrome P450 (CYP) enzymes play a vital role in the metabolism of most medicines and nanoparticles have the capacity to modulate. A previous study on the effect of porous silicon nanoparticles revealed that the enzymatic activity of CYP2D6 was the most susceptible to inhibition by the

porous silicon nanoparticles compared with other CYP isoforms in human liver microsomes. Also, aminopropylsilane-modified silicon nanoparticles have been known to inhibit the activity of CYP2D6 by 80%, regardless of nanoparticle concentration. The competitive, and non-competitive modes of inhibition, electrostatic interactions of nanoparticles with salts, and the nonspecific adsorption of lipids onto the nanoparticle surface are all possible explanations for these findings [48]. Figure 8 explains the role of CYP in nanoparticles.

Also, nanoparticle metabolic processes may differ significantly depending on the physicochemical features of the nanoparticles. The understanding of nanoparticle degrading mechanisms is currently restricted. Enzymatic and chemical degradation of biodegradable nanoparticles such as PLGA, protein, and lipid nanoparticles occurs, and the degraded products are eliminated in urine and bile. Nonbiodegradable nanoparticles, on the other hand, have a significantly slower metabolism. The accumulation of intravenously injected gold nanoparticles in the mouse liver was discovered, and the clearance process lasted more than 6 months [58].

In the case of silver nanoparticles, extracellular and intracellular dissolution were the two pathways carried out, releasing soluble silver species, and silver nanoparticles transforming into silver sulfide particles. Furthermore, under in vivo acidic and reactive circumstances, the physicochemical properties of nanoparticles may alter, making the degradation process even more unpredictable. Furthermore, in vivo nanoparticle aggregation may occur, complicating the process and altering the rate of disintegration. Because of the lack of knowledge of the chemical and metabolic degradation processes, most PBPK models assume first-order degradation kinetics for most nanoparticles. The nanoparticle degradation rate constant may be tissue-specific due to differences in pH, oxidative conditions, and enzyme activity in diverse tissues [59].

Elimination

To evaluate the clinical transition of nanomaterials and expedite their applications in disease theranostics, a thorough evaluation of their toxicity and metabolic behavior in the body has been conducted. Nanoparticle clearance in metabolic processes follows two basic mechanisms. Here, excretion is categorized into two groups: (1) hepatobiliary and fecal excretion; and (2) urine excretion [60].

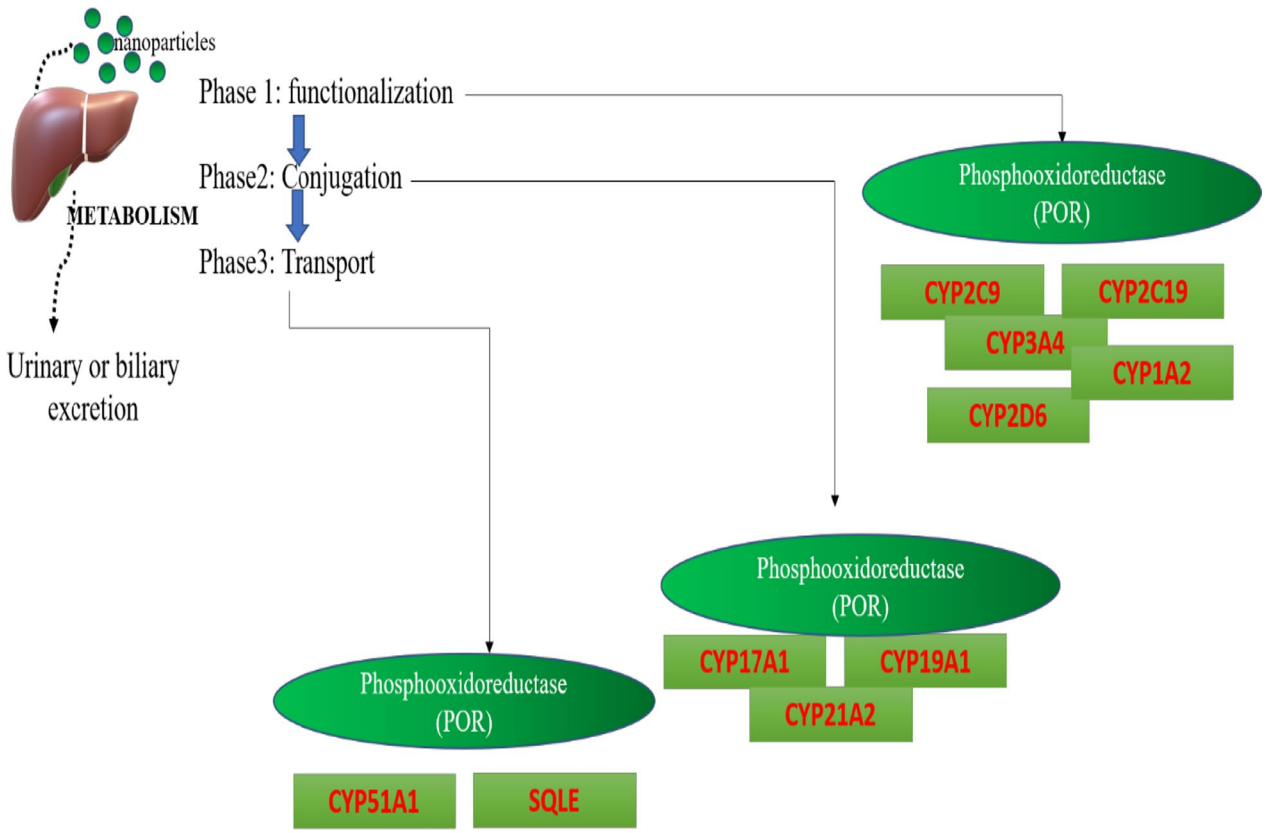


Fig. 8 Role of CYP in the metabolism of nanoparticle/ drugs

Intact nanoparticles or the byproducts of their breakdown can be eliminated in bile following hepatocyte digestion. Renal clearance is the most efficient way to eliminate nanoparticles because hepatobiliary excretion is known to be delayed, lasting from hours to months. Hepatocyte-targeting ligands can be added to nanoparticles to improve their hepatobiliary clearance if they cannot be removed through the kidneys or macrophages [61]. The differences in routes of renal clearance and hepatobiliary clearance are mentioned in Fig. 9.

Nanoparticles also interact with the glomerular capillary wall and may pass through the glomerular capillaries and enter Bowman's cavity before being reabsorbed by the renal tubule. At this point, some of the particles are returned to the bloodstream while other particles are excreted in the urine. In the kidney's glomerular basement membrane, research has found that a cationic cyclodextrin-based siRNA polymer can leak from glomerular porosity endothelial cells (GBM). Several negatively charged proteoglycans, including heparin sulfate, aid this process, and it is subsequently excreted in the urine. Some biodegradable nanomaterials may break down inside the body into metabolites with a low molecular weight that is excreted by kidneys [32, 62].

Pharmacokinetics of potential nanoparticles

Pharmacokinetics of gold nanoparticles

Gold's uses in nanotechnology have multiplied as its size has dropped, displaying new astounding properties, including strong resonant extinction, field amplification with optical manipulations beyond the diffraction limit, and ultrasensitive biosensing, among others[63, 64]. In biomedical applications such as tumor targeting and as contrast agents, gold nanoparticles have been used. They have also been used in confocal reflectance microscopy, photoacoustic tomography, optical coherence tomography, and imaging modalities [65, 66].The toxicity of gold nanostructures is governed by their size, shape, surface chemistry, which includes hazardous elements, surface charge, and stabilizing coatings.

Recent research involved the pharmacokinetic investigation of dextran-coated gold nanoparticles. The subjects' (mice) received a single intravenous injection of 1 mg/kg gold nanoparticle to evaluate pharmacokinetic action. After treatment with nanoparticles, the body weight and behavior of mice were evaluated to assess any possible detrimental effects. All animals exhibited no evidence of lethargy or indifference after receiving nanoparticles, and all appeared healthy and engaged in normal behavior. The semilogarithmic blood concentration–time curve demonstrated a sudden decrease in the initial concentration, followed by a gradual decrease, a rapid initial distribution phase, and a delayed terminal elimination phase. 24 h after injection, gold was no longer detectable in the blood, indicating a short half-life for elimination and a high clearance value. Due to nanoparticle transport to the peripheral compartment (tissues) and concurrent gold-dextran nanoparticle removal, the concentration of gold-dextran nanoparticles in the central compartment (blood) falls fast [67].

According to studies on tissue distribution, gold nanoparticles accumulate the most in the liver (35%) and least in the brain (0.03 ng/mg). In addition, it was inferred that the kidney did not commence clearance because 0.1% of the nanoparticle was detected in the urine, and there was no sign of atrophy, hyperplasia, necrosis, or inflammation. Plasma aspartate aminotransferase (ASAT) and plasma alanine

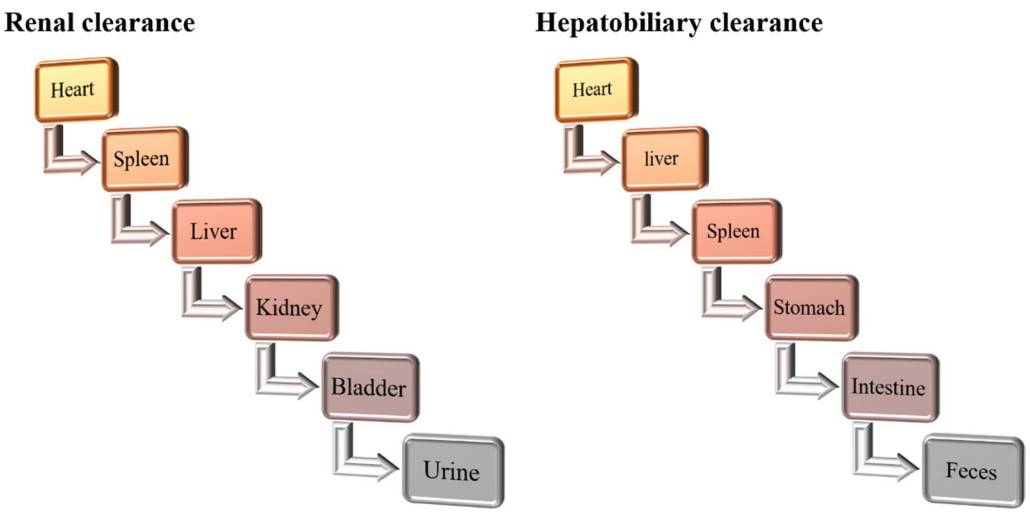


Fig. 9 Routes of renal clearance and hepatobiliary clearance

aminotransferase (ALAT) were tested to evaluate hepatocellular damage. The findings revealed that nanoparticles were collected in the liver but did not cause any harm to the individual. In order to investigate the potential inflammatory effect of the nanoparticle, 30 pg/ml of interleukin-6 (IL-6) was injected, however, no significant change in plasma level was observed [68].

Although gold nanoparticles have several benefits for biomedical applications, their broad adoption is hampered by insufficient and contentious toxicity data. Recently, polyethylene glycol-coated gold nanoparticles (PEG-AuNPs) were used in an in vivo toxicity assessment. The rat liver, lung, spleen, and kidney were studied for PEG-AuNPs' pharmacokinetics and biodistribution following a single intravenous injection (0.7 mg/kg) at various intervals. PEG-AuNPs collected mostly in the liver and spleen, where they stayed for up to 28 days following treatment, and they had a comparatively lengthy blood circulation period. Apoptotic-like cells in the white splenic pulp 24 h after delivery and increased cytoplasmic vacuolation in hepatocytes 24 h and 7 days after PEG-AuNPs exposure have been noted; however, 28 days post-exposure were no longer evident with altered changes in lipid metabolism and liver -injury markers [69]

A novel delivery method was created in which several drug moieties envelop each gold nanoparticle, enabling them to function as a cohesive unit against microorganisms and efficiently breach cell walls. Because of this property, gold nanoparticles can introduce many antibiotic molecules into cells at a highly targeted volume. Mesenchymal cells are principally responsible for the fibro obliteration of tiny airways in Bronchiolitis obliterans syndrome. Mesenchymal cell proliferation is effectively inhibited and apoptosis is increased by an engineered gold nanoparticle containing everolimus. Because they can penetrate cells, cyclic peptide-capped gold nanoparticles are an appealing and effective option for a drug delivery method. They vary in a number of ways from conventional gold nanoparticles, including the hydrophobic residues in the peptides. By interacting with hydrophobic residues, they are produced to disrupt and/or infiltrate cell membranes, allowing molecular payload to have a greater absorption than with traditional delivery [70]. Neither chemical functionalization nor covalent conjugation between biologically active molecules and capped nanoparticles is necessary for the surface with cyclic peptides. The peptide's hydrophobic amino acids creates a pocket where the medication can be noncovalently trapped. In cyclic peptides, the residues of amino acids function as both capping agents and concurrent reductants. When paired with antiviral and anticancer medications, linear peptides—which are amino acids that include nitrogen heteroaromatics, which are efficient metal binders and socan be utilized as possible scaffolds for the synthesis of noncovalent prodrugs [71, 72].

Pharmacokinetics of silver nanoparticles

To demonstrate the viability of the proposed techniques, animal and human kidney cells were used along with AgNPs (Silver Nanoparticles) of both positive (AgNPs+) and negative (AgNPs) charge at the appropriate concentrations and times, and the subsequent ADME elements were evaluated [73].

Despite several theories, the specific mechanism behind the antibacterial properties of silver nanoparticles has not been identified. It is well known that silver nanoparticles bound to a bacterial cell wall alter the structure of the cell membrane and membrane permeability, causing cell death. According to studies using electron spin resonance, another way that silver nanoparticles work is by producing free radicals that cause cell death. Free radicals have the capacity to damage cell membranes by causing membrane permeability when exposed to bacteria, ultimately resulting in cell death [74]. Researchers investigated 20 nm and 50 nm washed and unwashed AgNPs in pig skin during a 14-day period. After topical treatment, it was observed that AgNPs were exclusively present in the stratum corneum's surface layers [75].

It has also been shown that regardless of the exposure route, the liver is the primary organ for Ag distribution, followed by the spleen and kidneys. It has been found to accumulate in a variety of liver cell types, including Kupffer cells, hepatocytes, and sinusoidal endothelium cells. Another study reported silver deposition in all kidney regions, including the cortex, medulla, inner medulla, and cortical glomeruli [73].In another study, results reveal that after 28 days of repeated oral exposure to 14 nm PVP-coated or silver acetate, there was negligible.

silver excretion in the urine (0.1% of 24-h consumption), but there was a significant amount in the feces. This was caused by the lower bioavailability of silver nanoparticles [76].

In the pharmaceutical sector, AgNPs have been used as drug delivery vehicles. A recent work used a previously identified 3-methyl-1-phenylbutan-2-amine as a mebeverine precursor (MP) in an attempt to generate drug-loaded Ag NPs. Galactose was utilized to create a thin coating that encased the nanoparticles as a reducing and capping agent. With an excellent medication release of between 80 and 85%, these MP-loaded silver nanoparticles have emerged as a valuable therapy option for inflammatory bowel disease [77].

Recently, hyaluronic acid have been used as a stabilizing and reducing agent in a unique hyaluronic acid-based method for the environmentally friendly production

of silver nanoparticles. Lipid-based nanoparticles and liposomes are the other most researched carrier systems to improve drug delivery. They offer new ways to deliver drugs and highlight the use of recently developed nanocarriers for encapsulating and targeting active molecules in combination therapies, immunomodulation, and theranostics [78].

Pharmacokinetics of iron-oxide nanoparticles

Three crucial factors—pharmacokinetics, short- and long-term tolerability in vivo, and therapeutic or diagnostic efficacy in the target organ—are necessary for Iron Oxide Nanoparticles (IONP) to be successful in clinical trials. Despite extensive research, there are still open issues surrounding the formulation of IONP in terms of safety and therapeutic efficacy. A study looked at several antibodies conjugated with these IONPs to target heart injury. The findings showed that lipid-coated ultra-paramagnetic iron particles (LUSPIO) had a 30% longer blood half-life and improved absorption. It was observed that liver absorption of superparamagnetic iron oxide lipid-coated particles was 10–15% lower. Therefore, developing a standard database to classify diverse pharmacokinetic, biodistribution, and toxicity results based on IONP-specific traits and well-defined experimental parameters can assist researchers in locating the necessary information more quickly and effectively [79].

In the presence of plasma, IONP treated with polyethyleneimine (PEI) tends to form large aggregates rapidly. Moreover, PEG coating considerably inhibited IONP agglomeration in biological fluids, demonstrating superior colloidal stability. Another key factor affecting the destiny and biological effects of IONPs is their surface coating. A range of natural and artificial coating materials, such as dextran, Pluronic, and PEG, were used to increase the stability and blood circulation of IONPs due to their colloidal instability. Due to its strong steric hindrance and anti-fouling solid properties, which help to stabilize IONPs, PEG is the most often used coating polymer for IONP [80].

The pharmacokinetic characteristics of dendrimer-coated iron oxide nanoparticles were recently discovered. Co-precipitation was used to create IONPs, and the fourth generation (G4) polyamidoamine (PAMAM) dendrimer was applied to them. Iron levels in the blood and various organs, such as the lung, liver, brain, heart, tumor, and kidney, were assessed by inductively coupled plasma mass spectrometry (ICP-MS) at 4, 8, 12, and 24 h after injection to determine the biodistribution. The suspension was intraperitoneally injected into tumor-bearing BALB/c mice. Additionally, BALB/c mice were injected with various G4@IONP concentrations, and blood, renal, and hepatic variables were analyzed to further investigate the toxicity of G4@IONPs. Additionally, histological staining was done to determine how G4@IONPs affected the liver and kidney tissues. The findings demonstrated that 24 h after injection, the kidney, liver, and lung tissues had greater iron contents wherein blood urea nitrogen and direct bilirubin levels significantly increased at a dose of 10 mg/kg, according to toxicology evaluations. Additionally, liver tissue showed histological abnormalities in this concentration. This encourages the future investigation of IONPs in future biomedical applications [81].

Recent work involved a cationic peptide lasioglossin that was administered using bare iron oxide nanoparticles. They observed the lasioglossin binding patterns to the IONPs under various circumstances, including pH, buffer type, particle concentration, and duration. The drug loading in phosphate-buffered saline (PBS) was the greatest, at 22.7% [82].

A recent study used the co-precipitation approach to study the effects of co-coating magnetic iron oxide nanoparticles with polyvinyl alcohol and the anticancer medication sorafenib. The resultant nanoparticles showed a magnetite crystal structure. The information demonstrated that the coating of the magnetic iron oxide nanoparticles of the three compounds was successful. Furthermore, it was found to have no cytotoxicity toward normal fibroblast 3T3 cells and to have far superior anticancer activity against HepG2 cells and liver cancer than the medication sorafenib alone. It was discovered that the produced samples' superparamagnetic nature gave them exceptional magnetic properties. Additionally, it was discovered that the coating caused the particle size to drop to about 40 nm, and the size distribution narrowed and took on a consistent spherical shape. Remarkably, the drug's toxicity was much reduced by its magnetic nanoparticle creation when compared to its pure form. These results suggest that this technique can be employed to create magnetic nanoparticles for drug delivery, as these nanocarriers meet all the necessary criteria for exciting new biomedical uses.

It is necessary to conduct a thorough analysis of the effects of various additional molecular parameters on the pharmacokinetic performance and consistency of the IONPs, including the effects of mechanical flexibility or rigidity, molecular weight, density on the surface of the nanoparticles, and molecular structure of the coating molecules. Also unknown are the effects of iron oxide size, given dose, and crystal structure on their rates of oxidation in MPS macrophages and conversion to plasma ferritin [83]. To explore these effects more precisely, recently created characterization methods with better mass sensitivities should be used.

Pharmacokinetics of lipid nanoparticles

Lipid nanoparticles can be produced with particle sizes ranging from a few tens to a few hundreds of nanometers, just like the vast majority of nanoparticles. They can also be altered with hydrophilic, electrifiable, or active-targeting ligands to improve their in vivo performance. Here, Solid lipid nanoparticles (SLNs) play a critical function in the drug delivery system for proteins and insoluble medicines by dramatically altering drug molecules in vivo [84].

According to studies, SLNs can more effectively cross biological barriers because of their tiny size (50–1000 nm) and biolipid content. SLNs may affect the biodistribution and in vivo performance of loaded medicines. Like other colloidal drug delivery techniques like liposomes, micelles, and polymeric nanoparticles, they assemble in or target particular biological tissues or organs. SLNs have distinctive surface properties because of their lipidic compositions, which may lead to special interactions with biomembranes and biodistribution [85].

Most SLNs administered intravenously will build up in the liver, spleen, or lungs, where the vehicle's breakdown may take place. An enzymatic breakdown will lead to increased drug molecule release and SLN disruption. Despite their tiny particle size, SLNs increase adhesion despite lowering nasolachrymal duct clearance. Some SLNs will be destroyed in ways other than respiration once they reach the pulmonary alveoli. The inhaled material will start to move to nearby lymph nodes after deposition. This suggests that lymphatics may be targeted using pulmonary delivery or SLNs [86].

Few studies have been done on the pharmacokinetics of SLN administered by different delivery methods, including pulmonary, ocular, rectal, and subcutaneous route. Nebulizing celecoxib-loaded NLC showed a four-fold greater AUC in lung tissues than the celecoxib (Cxb) solution after the pulmonary injection of lipid nanoparticles. The pulmonary bioavailability of Cxb was increased by Cxb-NLC aerosolization in comparison to solution formulation [87].

Also, nanoencapsulation of SLNs with curcumin proved to enhance curcumin's bioavailability, extending its antitumor effectiveness and cellular absorption and boosting its chemical stability and dispersibility. The purpose of this research was to encapsulate curcumin into SLNs using both liquid and solid lipids in order to increase curcumin's aqueous dispersibility and stability, prolonging its anti-cancer action and cellular uptake, and improve its bioavailability. By combining a high-shear dispersion technique with heated, high-pressure homogenization, curcumin-loaded solid lipid nanoparticles (C-SLNs) were created. Particle size, zeta potential, drug entrapment effectiveness, drug loading, stability, and in vitro drug release kinetics are only a few of the physicochemical characteristics of C-SLNs that have been identified. Additionally, research was done on the cytotoxicity, cellular absorption in tumor cells, and in vivo bioavailability of C-SLNs in rats. It has been successful to create C-SLNs with enhanced chemical stability and dispersibility in aqueous systems. A curcumin delivery method with promise for application in treating cancer may be C-SLNs [88].

Research has reported their beneficial qualities, which include their ability to deliver controlled and sustained drug release, improve transcorneal penetration and enhance ocular bioavailability, and be biodegradable and biocompatible due to the generally recognized as safe lipid constituents, contribute to their increasing advancement in ocular therapeutics [89]. One of the studies compared the pharmacokinetics of lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) that were artificially broken down into lipolysates in conjugation with silymarin as a model drug. The lipolysates were produced by lipolyzing phospholipid- and bile salt-enriched simulated intestinal fluid, whereas the lipid nanoparticles were created using a traditional heat homogenization technique. The water-soluble form of mixed micelles could be created from more than 80% of vehicle-associated medicines. When compared to integral NLCs and SLNs, lipolysates' bioavailability was 74.86% and 59.09% lower in dogs, according to pharmacokinetics research. It was shown that the majority of medication absorption was facilitated by lipolysates. The advantage of integral nanoparticles over their lipolysate counterparts was minor; if the 20% of the medication that precipitated during in vitro lipolysis were subtracted from the total amount of absorption, the advantage of integral nanoparticles would be severely weakened. In conclusion, intact lipid nanoparticle contribution was minimal and lipolysis was the primary in vivo absorption pathway [18].

Impact of nanoparticles in the human body

Since several nanoparticles have already been used in numerous industrial processes and products, nanotoxicology has become increasingly popular. Concerns regarding the potential negative health consequences of nanoparticles and nanostructures have grown as the ways in which nanoparticles and living systems interact remain unknown. Particle complexity is increased by their capacity to interact with biological matter, attach to it, and change their surface properties in response to their environment [90].

The primary mechanism for the transfer of nanoparticles has been identified as endocytosis of alveolar epithelial cells. Inhaled nanoparticles can enter other organs through the lungs and olfactory bulb. Given that particles would have direct access to the central

nervous system via this channel can be neurotoxicologically dangerous [91].However, once they have gotten into the body and into the bloodstream, nanoparticles might have access to other organs. Natural bodily barriers like the blood–brain barrier, the materno-fetal barrier, and the air-blood barrier in the lungs receive a lot of attention. During biodistribution investigations, nanoparticles were found in the liver, spleen, heart, and brain at low amounts. The bioaccumulation of nanoparticles in numerous organs is another issue of concern. However, the remaining nanoparticles may excrete through urine and whether they bioaccumulate in particular organs, potentially impeding the body's excretion systems, are also unknown.

Interestingly, the immune system compatibility of nanoparticles is largely governed by their surface chemistry. Nanoparticles have long been known to have the ability to both stimulate and suppress immune responses. Cytokine production can be impacted by nanomaterials. According to research, nanoparticles may influence pro-inflammatory disease processes in the lungs, notably allergies, by inducing an oxidative stress mechanism. To assess the cytotoxicity, immunotoxicity, and genotoxicity of gold and iron oxide nanoparticles on human cells, numerous groups have used a battery of cell-based investigations revealing meager effects. However, additional research is required to develop and evaluate approaches for assessing the immunotoxicity of nanomaterials [92].

Also, animal studies have shown that nanometer-sized substances such as carbon, polystyrene, iron, titanium dioxide, and iridium can irritate the bronchi and alveoli. In exceptional cases, it has been shown that welding fumes containing nanoscale indium-zinc oxide and zirconium particles can cause inflammatory reactions in individuals who have been exposed to them at work. Numerous studies have been conducted on the effects of nanoparticles, and surface texture and biological effects are closely related. For example, 20 nm titanium dioxide (or nickel- and vanadium-dioxide particles) caused more inflammatory responses in rats and mice than particles that were 250 nm in size. These findings suggest that when considering toxicity, surface toxicity is more important than bulk. The possibility that inhaling nanoparticles could cause cancer is a serious problem. Rats exposed to high doses of granular, physiologically stable nano dust (inert bulk material) had an increased incidence of tumors. However, it is unknown whether this is due to the nanoparticles' direct genotoxic effect or secondary reactions such as the production of free radicals, as in chronic inflammation. It is now hard to determine how nanoparticles in low doses affect humans or whether they can cause cancer. Prior to scaling up a nanoparticle for additional biomedical uses, it is of utmost importance to evaluate its overall safety and efficacy at every stage [91]. Figure 10 gives an overall outlook of impact of nanoparticles in the human body.

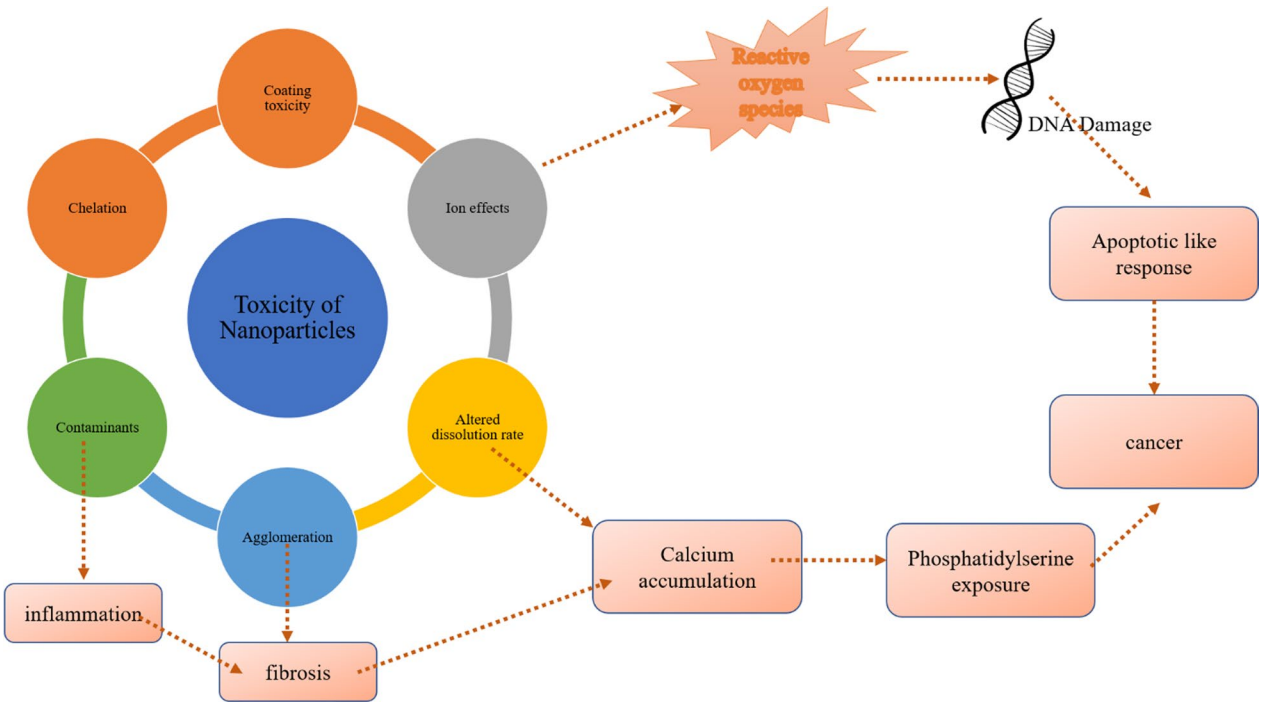


Fig. 10 Impact of nanoparticles on the human body and their plausible effects

Future directions regarding pharmacokinetics of nanoparticles

Early efforts in nanomedicine focused on improving the molecular properties of already existing therapeutic and diagnostic agents, but more recently, supporters of nanotechnology have tried to use cutting-edge therapeutic and diagnostic methodologies for the improvement of biomedical applications. Conventionally, synergistic drug combinations can be distributed ratiometrically, spatially, and temporally to the regions of pharmacological activity by using nanotechnology in drug delivery. Due to a better understanding of the molecular mechanisms driving specific therapeutic combinations and the utilization of nanosized drug carriers, several nanoparticle formulations of synergistic drug combinations have advanced to clinical trials [92].

The main focus of nanomedicine research for the past several years are the invention of novel nanoparticle systems and the characterization of their physicochemical properties in relation to their biological fate and functions. It is noted that the pharmacokinetics of medications encapsulated in nanoparticles differ from free pharmaceuticals in aqueous forms (longer half-life duration) [93].

Also, the potential of the drug and the upcoming pharmaceutical products are significantly influenced by many pharmacokinetic parameters. Therefore, it is necessary to evaluate applications based on nanomaterials using the same standards. These nanodrug approaches might be able to address issues in biopharmaceuticals, such as inconsistent drug release, poor stability, limited pharmacokinetic behavior, and active component toxicity. In order to increase the therapeutic payload of nanoparticles and lower their potential toxicity, more development is required. This requires a deeper understanding of the harmful mechanisms and physicochemical properties associated with them. Future collaboration between the pharmaceutical industry and academia could make nanoparticles a viable and secure nanodrug carrier alternative. With successful advancements in the safety, efficacy, and quality of drugs, we may still be a long way off from the ultimate goal of the nanodrug approach. [68]. Figure 11 depicts the comparative ADME profiling of drugs and nanoparticles.

Three fundamental mechanistic components are combined in the notion of nanotherapeutic delivery, each of which is believed to be crucial for effective delivery: Targeted cells absorb drug-carrying nanoparticles intracellularly, (i) selective cellular binding, (ii) controlled release of transported drug molecules. Although crucial to the development of nanotherapeutic delivery systems, the numerous drug release mechanisms that have been devised have not yet undergone a thorough molecular examination. Controlled drug release occurs through a cleavage of ester hydrolysis, amide hydrolysis, hydrazone hydrolysis, disulfide exchange, mannich bases and thermolysis [94].

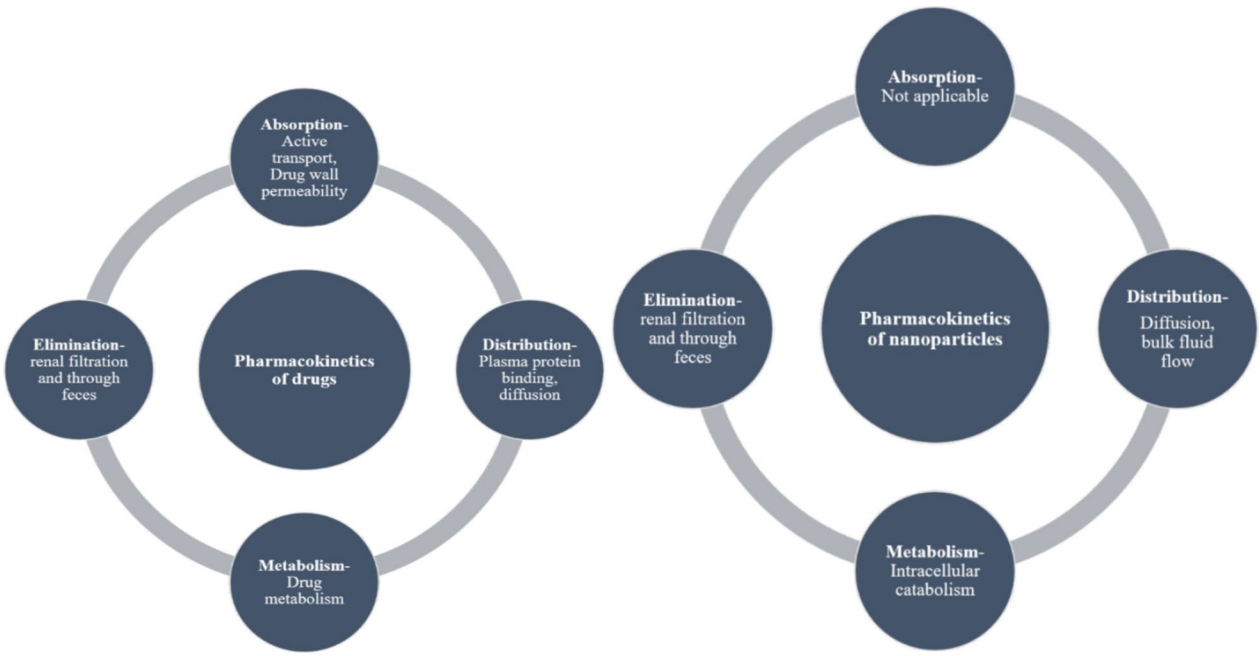


Fig. 11 Comparison of ADME profiling of drugs and nanoparticles

In the field of anticancer treatments, where nearly all chemotherapeutic drugs have one or more of these drawbacks, and nanotherapeutic delivery techniques have considerable promise to address these concerns. Due to their hydrophobic nature, many additional anticancer medications, including tamoxifen, 5-fluorouracil (5-FU), hydroxycamptothecin, and paclitaxel (PTX), are difficult to formulate in aqueous form. Studies have shown an effective release of doxorubicin from photocaged drug molecules transported by upconversion nanocrystals (UCNs) in deep tissues that are otherwise inaccessible to UV–Vis light was facilitated by their exposure to near-infrared light (NIR) [95, 96].

Regarding the pharmacokinetics of nanoparticles, immunological barriers pose an unresolved therapeutic challenge. Understanding the immunological compatibility of nanomedicine formulations and their effect on hematological parameters is currently regarded as a crucial step in the preclinical development of nanomedicines, as immunological adverse events account for 15% of early-stage therapeutic failure. Endotoxin or lipopolysaccharide contamination of the systems presents the greatest difficulty in immunologically characterizing nanoformulations. Nanoparticles can bind to this type of surface-adhering contamination due to their large contact surfaces. Endotoxin contamination is also responsible for numerous inflammatory effects of nanoparticles [97].

Nanoparticle immunogenicity is crucial because the immune system's interaction with the formulation might result in a range of outcomes. It may fail to perceive the particles as a threat and destroy them through renal filtration or phagocytosis. In other instances, an inflammatory response may be triggered, resulting in a prolonged inflammation that cannot eliminate the particles and injured tissues. Therefore, investigations must be conducted using in vivo models, as it is too challenging to detect immunological effects in vitro [13].

The use of nanoparticles in biomedical applications has increased at the same rate as their adverse side effects, which limit their safety. Therefore, the development of nanoparticles and the selection of nanomaterials as encapsulant systems with the objective of obtaining delayed release and improved pharmacological activity relative to conventional drug therapies. Due to the absence of a precise and universal international regulatory definition of these materials, their levels of toxicity, and the most effective methods for approaching and investigating them, these concerns have been identified during the development stages. Due to this, many nanoformulations encounter difficulties during preclinical testing, and subsequently, clinical studies face complex regulatory challenges. Despite the importance of nanomedicine to the pharmaceutical industry and the high aspirations for nanomedicine, there is little regulatory guidance in this field [13]. Table 4 details the comparative effectiveness of the pharmacokinetics of medicines and nanoparticles.

The nanoparticles exhibit a wide variety of features that may have an effect on their pharmacokinetics and, consequently, their toxicity balance; they are not the all-purpose "magic bullet" that was once believed. This could identify the various factors of pharmacokinetic variability, through identifying the ADME process [100].

Conclusions

The use of nanoplatforms for drug delivery has opened up new avenues for the distribution of medications as particulates, which specifically modifies the LADME profile. When creating suitable drug delivery systems based on nanomaterials for final clinical evaluations, accurate knowledge of the pharmacokinetics features related to the LADME is essential. This paper has focused on the pharmacokinetics of the nanomaterials and their ability to adsorb proteins, which is determined by the physicochemical characteristics of the nanomaterials. Therefore, to identify and anticipate the in vivo response of the nanomaterials further understanding of the relationship between their physicochemical characteristics and their interface with the body is yet to be resolved. With the help of this review,

Table 4 Comparison of features regarding the pharmacokinetics of nanoparticles and drugs [98, 99]

Pharmacokinetics of drug delivery system		Pharmacokinetics of nanoparticles	
Advantages	**Drawbacks**	**Advantages**	**Drawbacks**
High drug load	Optimization of protein delivery system	Narrow size distribution	Optimization of parenteral routes
Controlled release	RES overload	Many nanoparticles are stable in biological fluids	Immunological barriers
Regulation of pharmacokinetics	Host defense reaction	Bioavailability can be increased through cross-linking agents	Assessment of toxicity and other biosafety methods
Delivery of nucleic acids	Biological barriers	Specific drug targeting and delivery	Optimization of sustained release of drug-loaded nanoparticles

particular solutions will be developed, where pharmacokinetic parameters will aid in selecting whether or not to adopt them in biomedical applications and pave the way for future therapeutic evaluations. A critical evaluation of these ideas have been presented, along with an integrated viewpoint based on the latest engineering and design of nanocarriers using nanoscience methods. With several regulatory-approved medications already on the market and numerous others undergoing late-phase clinical studies, this industry has a bright future ahead of it. The development of tailored nanomedicines can progress further with simultaneous advancements in comprehensive computational knowledge of the genomes and epigenomics of interindividual variability in drug responses. This will open the door for significant scientific investigation and human use validation.

Abbreviations

LADME	Liberation, adsorption, distribution, metabolism, and elimination
IVIVE	In vitro-in vivo extrapolation
PBPK	Physiologically-based pharmacokinetic
ADME	Adsorption, distribution, metabolism, and elimination
EPR	Enhanced permeability and retention
BBB	Blood–brain barrier
PHDCA	Pegylated polyhexadecylcyanoacrylate
PDI	Polydispersity index
RES	Reticuloendothelial system
PK	Pharmacokinetics
TK	Toxicokinetics
MPS	Mononuclear phagocyte system
ASAT	Aspartate aminotransferase
ALAT	Plasma alanine aminotransferase
IONP	Iron oxide nanoparticles
PEI	Polyethyleneimine
PEG	Polyethene glycol
SLN	Solid lipid nanoparticles
NLC	Nanostructured lipid carriers

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Author contributions
Dr. KS conceptualized the work on pharmacokinetics of nanoparticles and performed a formal analysis of every step. The project administration and concerns regarding the resources were provided by Dr. KS. Ms. MH proceeded with the acquisition of data regarding the pharmacokinetics process of all nanoparticles. Ms. MH was involved in manuscript preparation, followed by drafting the work. After a series of critical evaluations, the raw data were converted into a manuscript, overseen and validated by Dr. KS. All authors have read and approved the manuscript.

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