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Nanoparticles as Drug Delivery Systems: Benefits and Toxicological Concerns

[1]Sarmad Mohammed Hashim,

[2]ZuhairAbdulkareem Dawah

[3] Ban, M. A.

College of Veterinary medicine, University of Baghdad, Baghdad, Iraq.

sarmad.mohammed1206h@covm.uobaghdad.edu.iq

Zouher.kareem1206h@covm.uobaghdad.edu.iq

ban.manaf1206h@covm.uobaghdad.edu.iq

I. Abstract

The emergence of nanoparticles as a potential form of drug delivery system is because of its distinct physicochemical characteristics such as small size, high surface area, and surface characteristics that are tunable. These characteristics make it possible to achieve better solubility of drugs, targeted delivery, controlled release and better bioavailability. Liposomes, polymeric nanoparticles, and metal-based nanomaterials are examples of nanoparticle-based carriers that have shown a high potential in overcoming biological barriers, including the bloodbrain barrier and the tumor microenvironment. Consequently, they have been extensively studied in cancer and cardiovascular diseases, neurological disorders, and infectious diseases. Nevertheless, even with these benefits, there are significant toxicological issues when it comes to the use of nanoparticles. Their minute size enables them to engage with cellular constituents with the probability of triggering oxidative stress, inflammation, DNA damage, and organ toxicity. Particle size, shape, surface charge, composition and dose are some of the factors that play a significant role in altering the bio-distribution, pharmacokinetics, and toxicity profile in the body. The build-up in essential organs like liver, kidneys and lungs can cause undesirable effect and long-term safety and clearance processes have not been well studied. Thus, it is necessary to have a balanced appraisal of both the therapeutic advantages and the possible hazards of the nanoparticle-based delivery systems of drugs. Nano-toxicology, surface engineering, and biocompatible materials should be advanced and will play a pivotal role in enhancing safety and clinical translation. It can be recommended that future studies be aimed at optimization of nanoparticle design,

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standard of toxicity evaluation and development of regulatory guidelines to make sure that nanoparticles are safe and useful in medical practice.

Key word: Nanoparticles, Drug delivery, Nano-toxicology, Targeted therapy, Biocompatibility

II. Introduction:

Nanoparticles are submicron-sized delivery systems that can encapsulate a drug and regulate its pharmacokinetic and biodistribution profile. Commercially available drug-delivery nanoparticles take advantage of one or more of four strategies: (a) controlled, sustained release, (b) improved targeting to a pathologically relevant tissue or cell type, (c) the ability to cross a biological barrier, and (d) a biodistribution profile that minimizes toxicity to excess tissues. Nanoparticles can circumvent the blood–brain barrier (BBB), mucosal barriers, transdermal barriers, and the tumour microenvironment [1,2].

The delivery of therapeutic agents in general is becoming clinically relevant. Compounds that have poorly soluble, permeable, or stable drug characteristics are now being tested in the clinic because of delivery systems that increase the effectiveness and broaden the therapeutic window of the compound from conventional levels. Compounds considered to be safe therapeutically no longer require undesirable or ineffective lead-optimisation cycles compared to when they were originally registered in the early 1980s [3,4].

2. Fundamentals of Nanoparticle Drug Delivery

Nanoparticles selectivity deliver therapeutic and genetic agents to diseased cells while restricting distribution to healthy cells. They have been designed to overcome biological barriers and present drugs in pharmacologically active forms. Important design features include evasion of protein adsorption and opsonization, distinct biodistribution profiles, and transport through porous tissues. Nanoparticle-based drug carriers offer several potential advantages over conventional delivery methods [5]. They enable the administration of drugs with narrow therapeutic windows, such as those used against human immunodeficiency virus (HIV), in a safer manner. Nanoparticles help to progressively releaseantimycobacterial drugs that are effective against tuberculosis within intracellular vacuoles [6]. They promote and prolong the therapeutic efficacy of poorly water-soluble compounds, such as anticancer agents, that are otherwise rapidly eliminated after intravenous injection. Drug-loaded nanoparticles readily penetrate physiological barriers, such as the blood-brain barrier (BBB), mucosal membranes,

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and the tumour microenvironment, which severely impede the biodistribution of non-particulated molecules. Treatment of bacterial or viral infections can be performed locally to avoid underdosing and spread of infections. Formulations containing a large library of drugs can be screened to pinpoint the optimal candidate before selection of the formulation follows [7,8].

2.1. Classification and Characteristics

Nanoparticles can be classified in several ways, such as according to their nature (organic–inorganic), origin (natural–synthetic), shape (spherical, tubular, and plate-like), and others. Drug delivery nanoparticles are generally classified into two broad categories—lipid-based and polymer-based nanoparticles. Lipid-based nanoparticles include liposomes, micelles, nanoemulsions, and solid lipid nanoparticles, while polymer-based nanoparticles include polymeric micelles, hydrogels, and nanospheres. Other types of nanoparticles that have been used or investigated in drug delivery applications include dendrimers, silica, and gold nanoparticles [9,10].

The physicochemical properties of nanoparticles are crucial determinants of their interactions with biological fluids, cells, and tissues. Important characteristics that govern their behavior are size, shape, surface properties, porosity, charge, loading capacity, and the stability of their identity [11]. Nanoparticle drug carriers range in diameter from a few nanometers to several micrometers. A particle size of 1–100 nm is generally accepted as the nanoscale range. Nanoparticles larger than 100 nm are excluded from the blood capillaries and are therefore not expected to reach the cytoplasm of living cells unless the integrity of cells is impaired, which is rarely the case in normal physiological conditions [12,13].

The particles can be spherical or non-spherical, The shape influences biodistribution, clearance rate, and cellular uptake. It has also been shown that non-spherical particles have a higher tendency to aggregate during storage compared to spherical particles. Shape also influences the binding of particles to cells [14,15].

The surface of nanoparticles is normally covered with one or more surfactants containing hydrophobic or amphiphilic functionalities. The properties of nanoparticles depend not only on intrinsic factors, such as particle size and shape, but also on these surface characteristics. These properties also significantly affect functionalization. Surface characteristics determine the protein adsorption behavior of the particles after their injection into the body, thus influencing their circulation time in the blood and specific tissue targeting. Nanoparticles with a high surface-

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to-volume ratio are more effective in adsorbing molecules from the surrounding medium. Surface modifications are also required to facilitate the functionalization of nanoparticles [16,17].

Nanoparticles carry drugs either in the surrounding medium or within the polymeric matrix. Some particles are designed to release their payload in response to specific stimuli, such as pH, temperature, redox potential, and light, while others show a more traditional release behavior. The ability of nanoparticles to deliver drugs that are otherwise difficult to administer depends on the formulation technology, release kinetics, and physicochemical properties of the actives. Lipophilic drugs are delivered by lipid-based nanoparticles, while hydrophilic macromolecular drugs require polymeric systems. Stability in biological environments is essential to retain the effects of pre-formulated drugs. Formulations that undergo premature leakage may fail to show the anticipated advantages [18,19].

Nanoparticles in drug delivery systems can be configured for either passive or active targeting. Generating passive targeting exploits biological barriers and microenvironments that are inherently different between healthy and diseased tissues or at different points of disease progression. In the case of active targeting, target-specific recognition ligands, such as peptides, proteins, oligonucleotides, or small molecules, can be covalently attached to nanoparticles. It also forms part of the preformulation characterization that is crucial for scaling up production. Nanoparticle drug delivery systems have been used in a number of applications, mainly for cancer treatment [20,21].

2.2. Mechanisms of Cellular Uptake and Biodistribution

Cellular uptake and biodistribution represent critical determinants of the therapeutic efficacy of nanoparticles. After administration, nanoparticles circulate in the bloodstream until they reach a target tissue. They may then cross architectural barriers to enter target cells, where they release their cargo. During this process, however, nanoparticles are exposed to blood proteins that may opsonize them, rendering them susceptible to uptake by the mononuclear phagocyte system (MPS) and/or preventing their extravasation into target tissues [22]. In the case of the blood–brain barrier (BBB), nanoparticles oscillate between the vascular compartment, where they are exposed to the protein corona, and the astrocytic and pericytic space, the latter of which serves as the main–main entry point into the brain parenchyma. Ultimately, clearance will result in the irreversible loss of the administered drug and will be influenced by the initially administered dose, the granulometric distribution of the nanoparticles and their debris, and the physicochemical characteristics of both the nanoparticles and the released drug [23].

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Biological delivery is mediated by specific mechanisms and pathways that operate from the moment of administration until disposal of the drug. These pathways determine the residence time of the drug, any potential accumulation in irrelevant organs, and the possibility of reaching specific target sites. Hence, effective design of special delivery systems must account for these pathways and consider mechanisms of crossing biological barriers and subsequent release of the therapeutic agent from the carrier. Nanoparticles can therefore be used to cross delivery-restricted barriers, including the intestinal mucosa, the BBB and the placental barrier [24,25].

2.3. Design Considerations for Therapeutic Efficacy

Nanoparticles can deliver drugs to target tissues, enabling controlled release and improving therapeutic effects while reducing systemic toxicity. Therapeutic efficacy can be enhanced with rational design of the nanoparticles. Strategies include selection of appropriate targeting ligands, controlled release kinetics, and stabilization of the drug–nanoparticle complex against premature degradation in the biological milieu [26]. Scalable production methods should be identified, and any regulatory constraints imposed by specific characteristicssuch as particle size, shape, surface charge, or polymer composition considered [27].

3. Benefits of Nanoparticle-Based Delivery

The future of drug delivery systems based on nanoscale carriers has a great potential to surmount the challenges affecting the rapid translation of drugs in the laboratory to the clinic. With drugs prepared in nanoparticles or solid lipid nanoparticles the pharmacodynamics and pharmacokinetics of the drug can be enhanced over the traditional systems, and targeted tissues are selectively accumulated and extended circulation times [28]. These nanocarriers can facilitate controlled and sustained release of entrapped agents, reduce systemic toxicity and enhance therapeutic index, and enable transport across biological barriers such as the blood–brain barrier, mucosal barriers and barriers posed by the tumor microenvironment [29].

Nanoparticle formulations can also proactively accelerate the development of new therapeutics, such as small molecules, biologics, peptides or combination therapies that may otherwise lack commercial viability. Such formulations can improve the success rate and speed of clinical development by capitalizing on drugs with well-characterized pharmacology for which the most urgent need is the development of a delivery system. Nanoparticle formulations also constitute an efficient means of repurposing off-patent drugs—small molecules, biologics or

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biologics—that lack patent protection and have no commercial incentive, though substantial medical needs may still exist [30,31].

3.1. Enhanced Pharmacokinetics and Targeting

Nanoparticle-based formulations can significantly enhance the pharmacokinetic profile of therapeutics. They increase circulation time, thereby boosting the accumulation of drugs in target tissues for effective treatment. Nanoparticles can exploit the enhanced permeability and retention (EPR) effect observed in many tumors to facilitate selective accumulation at target sites. Passive targeting benefits a wide range of therapeutics, from small molecules to macromolecules. Additional active targeting strategies further improve the delivery of specific drugs by covalently modifying the surface of nanoparticles to include precise ligands, such as antibodies, peptides, nucleic acids, or small molecules [32].

3.2. Controlled and Sustained Release

Nanoparticles are able to provide both local or systemic release profiles, which corresponds to drug absorption and distribution on demand, and reduce side effects through protection of drugs till target cell access [33]. There are two significant processes that regulate release diffusion and degradation. The diffusion-controlled systems release the drug by movement of the drug at the interior location to the exterior environment, where the rate of release is a parabolic time-dependent function [34]. In degradation regulated systems, release is proportional to polymer degradation and the rate depends on such factors as molecular weight, the extent of crosslinking and the quality of the solvent; the active agent is released only when the polymer is fully degraded. The environmental variations (pH, temperature, ionic strength, glucose concentration) are used in stimulation-responsive delivery methods to induce drug release and thereby maximize therapeutic window [35].

3.3. Reduced Systemic Toxicity and Improved Therapeutic Window

Systemic toxicity of a drug is often closely related to its therapeutic window which is described as the difference between minimum effective plasma concentration and minimum toxic plasma concentration. With traditional formulations of drugs, there are high chances of off-target effects and unwanted toxicity. On the other hand, the drug delivery mode can decrease interactions with normal cells by targeting drugs with nanocarriers, thus reducing the adverse effects [36]. The problem of using many FDA-approved medicines with severe toxic side effects to their usage is crucial and demonstrates a critical requirement in the field of nanomedicine which is translational [37].

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3.4. Ability to Bypass Biological Barriers

By use of nanoparticles drugs can increase the capacity of drugs to penetrate the body and rudely bypass biological barriers that drugs face when administered. One of these barriers is the blood-brain barrier (BBB), which many therapeutic agents are not able to cross, severely restricting the therapeutic options of diseases of the central nervous system (CNS) [38,39]. The mechanisms by which these substances are made unable to cross the membrane remain under study but a promising approach currently in development to assist them to overcome this limitation involves nanoparticles being coated with certain ligands that have the ability to bind to receptors on the BBB endothelial cells [40]. Mucosal delivery, another possibility that has gained traction recently, offers a less invasive approach for the introduction of medications that are typically administered through injection. Nanoparticle systems that boost drug permeability across mucosal barriers (e.g., nasal, ocular, pulmonary, gastrointestinal) via the addition of specific bioadhesive polymer-based mucoadhesive materials have been developed to circumvent this restriction. Similarly, strategies for enhancing penetration of therapeutics through the dense extracellular matrix (ECM) of tumors and the tumor-cell infiltration of nanoparticles have been proposed to improve efficacy against cancers [41].

4. Toxicological and Safety Considerations

Development of successful nanoparticle-based delivery systems depends on rigorous examination of their toxicological implications to ensure patient safety. Safety investigations collected in accordance with Good Laboratory Practice (GLP) [42], assess both acute and chronic toxicity profiles. Acute toxicity studies compile information about potential organ-specific damage, dose–response relationships, and duration of effects to identify relevant biomarkers and determine volume-limited doses [42].

Long-term and chronic toxicity profiles may emerge with multiple nanomedicine administrations and are typically evaluated in conjunction with pharmacokinetic (PK) and physicochemical studies. Organ exposition, transfer routes, and parent compound persistence can inform the hazard category assigned to a formulation or compound [43].

4.1. Acute and Chronic Toxicity Profiles

Nanoparticles administered via different routes (i.v., i.m., etc.) can cause acute toxicity effects on different organs, such as the liver, lungs, heart, kidneys, spleen, and brain. Liver injuries are the most common acute effect reported so far, followed by lung injuries and cardiac injuries. The half-maximal lethal dose (LD50) of different nanoparticles of varying size exhibits a bell-shaped dose–response relationship between size and toxicity at acute exposure [44].

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Other studies show that longer exposure time leads to slightly higher toxicity levels. Tissue-resident macrophages play a key role in the acute post-dose toxicity of nanoparticles. Effect duration for excretable nanoparticles (after stopping dose) is generally 5-7 days. For non-excretable nanoparticles, toxicology returns to baseline but impacts (e.g. hepatic, pulmonary) remain detectable; the biological fate of these nanoparticles is still under exploration. Evaluation of acute toxicity is still essential for drug development: imaging agents, radionanoparticles and more [45,46].

4.2. Immunogenicity and Inflammatory Responses

Nanoparticle-based vehicles for drug delivery can elicit immunogenic and inflammatory responses that complicate safety and risk assessment. Immune responses to nanoparticles are initiated primarily by the innate arm of the immune system, which recognizes foreign materials or particles by pattern recognition receptors. Immune distribution, an early compartmentalization process that dictates collection and clearance from blood circulation, is also determined by the innate immune response [47]. Opsonization, the binding of biological molecules such as antibodies or complement proteins, occurs after the nanoformulation enters the blood and is another characteristic feature of the innate immune response. Immune responses can also occur when antigen-presenting cells such as dendritic cells, located in peripheral organs, capture the drugs or the carried drug particles introduced or delivered by nanoparticles. The development of a hypersensitivity response is a late component of the immune response after the establishment of an immune distribution phase in the presence of the drug or packaging nanoparticles [48].

Biodistribution, the second major factor influencing particle fate, is affected by organ clearance (i.e. excretion via urine or bile) and accumulation in various organs. Finally, the sensitivity or “hardness” of different biological barriers and the ease of disassembly of the nanoparticles under physiological conditions also govern the accessibility of the cargo to the cytosol [49].

4.3. Nanoparticle Composition and Surface Chemistry

The characteristics of nanoparticles determine the interactions with the biology, distribution, persistence and degradation, thereby affecting safety. The composition of materials dictates the products of the degradation process, the main materials that interact with biological systems. Coatings on surfaces, either deliberate (e.g., PEGylation to increase circulation) or accidental (e.g., biopersistence due to proteins in the physiological environment), control the extent of cellular uptake, internal mobilization, immunogenicity, and biopersistence and even therapeutic efficacy.

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The interaction of nanomaterials with biological systems leads to the creation of a so-called protein corona that can significantly modify the surface properties and influences the stability and clearance in vivo. These changes, however, are not well defined and may end up with a final formulation that is not in line with what was intended and well evaluated [50,51].

Surface functionalizations of nanoparticles (e.g., PEGylation, addition of surface proteins, charge modification, pH or ion sensitivity) seek to improve physiological targeting and retention time. Before clinical use, it is important to characterize modified particles, including quality and consistency of manufacturing. The decisions should be made based on a balance of biological reactions, the delivery site, material characteristics, the disease condition, and immune clearance. However, with the promising developments, not many nanoparticles have been approved by the FDA, which highlights the difficulties of converting experimental results into practice [52,53].

4.4. Clearance, Accumulation, and Long-Term Fate

The delivery of drugs by nanoparticles has received a lot of criticism due to its possible toxicological effects and safety risks. Chronic toxicity research on the polylactic acid (PLA)-based nanoparticles administered by the intravenous route to mice revealed no organ destruction and blood tests revealed normal physiological functions. However, investigations of other classes of nanoparticles indicated multiple organs accumulated substantial quantities following parenteral administration and displayed chronic phase toxicity. Following a single intravenous dose of gold nanoparticles, X-ray fluorescence imaging shows foreign material accumulating in the liver, spleen, lung, kidney, and gastrointestinal tract within 24 hours. The gold signal remained throughout a 60-day study. Three poly(lactic-co-glycolic acid) (PLGA) formulations—uncoated nanoparticles, chitosan-delivered nanoparticles, and chitosan nanoparticles labeled with a fluorescence dyewere assessed in mice as tested on alternative days for 30 days [54,55]. Minor accumulation was observed at different time points, and fluorescence signals dropped quickly after 1, 3, and 6 days. The particle was greatly cleared from the lung and spleen after 6 days, although very weak fluorescence signal remained in the kidney. Microscopic images displayed very weak signals in pharyngeal lymphatic and gastrointestinal tract tissues. Majority particles resided in macrophages indicated by overlaid images. Chitosan-made particles were detected in the reticuloendothelial system (RES) organs (spleen and liver) after 1 day, and almost complete clearance happened after 10 days. Non urea polymer coating helped to transfer particles from the pharynx into the digestion tract with unspecified polymer configuration, the excreted florescence signal was feeble around 10 days [56,57].

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Macrophages played a crucial rule, which impacted particle biodistribution and fate in the living body following intravenous routes. Data concerning excretory routes alongside long-term persistence of polymer-based nanoparticles following IV-injection are difficult to arrange, and researchers are subjected to lots of preclinical study on absorption, distribution, metabolism and excretion (ADME) of various polymers in the literature [58,59].

4.5. Species Differences and Translational Challenges

Preclinical animal studies are essential for assessing the safety of drug delivery nanoparticles prior to clinical research. However, clinical translation of formulations remains challenging because animal studies do not sufficiently predict delivery efficacy and toxicity in humans [60].

Extrapolation of therapeutic doses and safety margins are complicated by physiological differences between preclinical species and humans [61]. Nanoparticles have different clearance pathways depending on species, which may alter circulation half-lives and bio-distributions. Particle size, material properties, and surface modifications that affect circulating half-lives differ in their relative importance among species. For example, particles greater than 200 nm tend to exhibit rapid clearance through hepatobiliary routes in mice and rats, whereas particles around 100 nm evade this clearance pathway in these animals. These preclinical models thus hold limited predictive value for human particle delivery formulations [62].

Sterically stabilized or stealth particles designed to enhance payload delivery often fail to improve therapeutic efficacy in preclinical species. Particles exhibit smooth surface topographies and size distributions that promote unpredicted bio-distribution, which are introduced during synthesis in organic solvents and are retained even after extensive ligand exchange in aqueous media [63].

5. Risk Assessment and Regulatory Perspectives

Nanomaterials for drug delivery pose potential hazards not present in standard drug candidates. Differences in physicochemical properties challenge conventional preclinical assessments and risk evaluation practices [64,65].

As a general rule of thumb, intravenous administration of 1 mL of fluid per kilogram of body weight per hour corresponds with the maximum renal clearance rate for conventional drugs. For nanomaterials, however, a dosage of 0.1 mL per kilogram per hour is often considered administratively acceptable. Even so, formulations employed in laboratory trials seldom reach preclinical development or higher levels in drug approval. A quality by design

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approach encompassing safety and other properties is essential to produce nanomaterials acceptable for human trials [66].

5.1. Preclinical Evaluation Frameworks

The nanoparticle formulations have a preclinical evaluation system with some fundamental modules. These include in-depth physicochemical characterization, toxicity studies, pharmacokinetics and ADME, bio-distribution, and safety pharmacology [67]. Physicochemical characterization is a preliminary step before any other study, and involves the production of a physiologically relevant profile of therapeutic formulation. Toxicological assessments typically require the evaluation of various organ-specific exposure durations after a single dosing. The battery of organ-specific endpoints generally examined across preclinical studies is determined by the intended clinical application and route of administration of the nanoparticle system [68].

5.2. Analytical Characterization and Quality Control

Nanoparticle characterization encompasses the determination of relevant physicochemical parameters to ensure the reproducibility of in vitro and in vivo studies, the consistency of the manufacturing process, and the shelf-life of the formulation. Characterization is essential for risk assessment, and regulatory guidelines point to the need for a comprehensive physicochemical profiling, although the relevant sets of initial parameters remain undetermined [69].

Extensive chemical and physical modifications can considerably change the physicochemical properties of nanoparticles by altering their structure and chemical composition. For this reason, according to the FDA and EMA, it is critical to demonstrate lot-to-lot consistency [70]. Extensive physicochemical characterization of the final formulation following synthesis or chemical modification is also required to anticipate and later confirm the drug release profile of the carrier [71].

5.3. Regulatory Guidelines and Safety Thresholds

Regulatory bodies are focusing on comprehensive toxicological and physicochemical information in order to ensure that nanoparticles are safe to deliver drugs and therapy. Materials that are safe to human use are given priority. Moreover, the current legislative frameworks on environmental risk assessment can be usually incorporated in nano-medicine [72]. Although various international and intergovernmental guidelines address the resultant human toxicological exposurethe complete absence of simple, harmonized oversight documents has hampered nanoparticle

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development in certain jurisdictions. Accordingly, exposure scenarios have been proposed to enable broader risk assessment estimates [73].

Despite the lack of specific guidelines, several organizations stipulate fundamental principles governing the safety evaluation of pharmaceutical nanoparticles: products must be characterized, and their potential risks identified. Manufacturers are expected to safeguard the nanomedicine within its original protective coating and actively communicate any changes affecting potential risks. More precisely, information is required on the raw materials employed, the danger of decomposition, and the characteristics of debris and non-safeguarded molecules. ligands intentionally designed to induce biological action, and non-degradable nanoparticles are all classified as seriously hazardous. Therefore, constructive dialogue between scientists, manufacturers, and regulatory agencies is essential. Once human exposure has been established, pharmacovigilance and long-term study become mandatory. Labelling, immediate post-approval, long-term post-approval, and active post-approval are four categories of labelling requirement proposed [72,73].

6. Strategies to Mitigate Toxicological Risks

Long-term exposure to toxic nanoparticles, including those used in drug-delivery systems, remains a global health concern. Preclinical studies have evaluated the toxicity of lipid nanoparticles, polymer nanoparticles, micelles, exosomes, and metal nanoparticles, among others. The European Commission has proposed a nano-specific definition to establish a regulatory framework for nanomaterials. The need for toxicological profiles is widely recognized, yet testing remains limited. Nanoparticles not only reduce toxicity but also enable the encapsulation of toxic drugs. Safe-by-design principles must be incorporated from the outset to fully exploit their therapeutic potential [74,75].

Nanoparticles used in biomedical applications emphasize the remarkable importance of toxicological evaluation. Toxicity can be affected by the particles themselves, degradation products and surface characteristics. Nanomaterials can either cross the blood -brain barrier or be trapped in certain organs, and monodisperse nanoparticles are preferable in the study of toxicity. Prolonged exposure, be it dietary, atmospheric, or through pharmaceutical routes should be investigated seriously. At-risk populations Preclinical testing on at-risk populations has essential information on risk assessment [76].

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6.1. Material Selection and Biocompatibility

To enhance the therapeutic index, it is necessary to develop effective drug delivery systems, which will reduce the toxic effects on normal cells. Material selection is one of the key considerations to achieve such a goal. Along with the physicochemical properties of nanoparticles, including the size, shape, charge, and solid-state properties, some other factors must be taken into account as well [77].

Toxicological studies on established materials/polymeric systems demonstrate that toxicity issues remain a significant concern. Some nanomaterials previously considered biocompatible may still be toxic due to size, shape, surface chemistry, and aggregation [78]. A comprehensive understanding of the effects of nanoparticles on living systems, from a physicochemical perspective, is required to ensure safe design. Furthermore, new testing methods are needed to evaluate nanomaterials during the development stage and in association with commercial products. These considerations still require significant effort in medical applications, especially for conditions such as Parkinson's disease [79].

6.2. Surface Modification and Stealth Properties

Correlating nanoparticle drug carriers with stealth properties has the objective of preserving their circulation time. On the one hand, stealth biopharmaceuticals equilibrate rapidly with blood and extravasate from circulation through endothelial gaps. In contrast, stealth nanoparticles remain entrapped within the vasculature of certain anatomical compartments over extended intervals. The goal of modifying the surface of nanoparticles is two-fold, namely, to enhance the grip on the vasculature throughout the delivery period and to augment the entrapment in a given organ [80].

In preparing anticancer agents based on pH-sensitive liposomes, formulations underwent modification to hinder the onset of protein aggregation. Antibodies directed against macrophage receptors had a predictable adverse effect on therapeutic efficacy due to their induction of macrophage-mediated clearance. To ensure that anti-receptor or anti-target functionality was not lost, the degree of surface functionalization with thiolated polymer additional to a targeting lipid required close monitoring. Sustained surface-attached polymer remained on the liposome and shielded these particles substantially from the macrophage surveillance system [81].

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Surfactant-stabilized liposomes took several days to transition from a fluid state to a gel phase at body temperature provided that physiological pH or saline was used. Even after achieving a gel state, these liposomes were not yet suitable candidates, since the elongated and rigid shape of the particles inspected with an electron microscope did not allow good alignment in sufficiently wide elliptical cavities [82].

6.3. Dose Optimization and Exposure Modeling

Therapeutic index models may be employed to anticipate the safety margin for a given dose of a nanoparticle-based product. Accurate prediction of the relationship between exposure and adverse effects is essential to establish dose recommendations for preclinical studies. Different scenarios for human exposure can be modeled to delineate potential target organs, providing guidance on the evaluation of safety or adverse effect biomarkers [83].

6.4. Monitoring and Post-Market Surveillance

Development of a drug formulation does not cease with the grant of marketing authorization. Continued monitoring of the product during the post-market phase is essential, especially for pharmaceuticals with complex formulation characteristics and a novel mechanism of action. Nanoparticles exhibit such characteristics, and the importance of integrated post-market pharmacovigilance has been recognized in numerous advanced economies [83].This entails not only vigilance to evaluate the occurrence of adverse events associated with the governance, formulation, and physical quality of medicines and the integrity of administration practices but also a wider data-gathering programme that provides information on the dynamics and heterogeneity of nanomedicines, elucidates the influence of biophysicochemical characteristics on in vivo behaviour, and enables comparisons with preclinical models [84].

Post-market pharmacovigilance highlights systemic and organ-specific adverse effects. Real-world data on biodistribution, drug release dynamics, therapeutic activity, and undesirable side effects during routine use can clarify how particle parameters correlate with drug performance and safety following administration to humans and other species. Synthesis of structure–safety relationship information across species can thus underscore the translational aspect of preclinical modelling, identify potential safety signals earlier in the design process, and ultimately guide the design of next-generation formulations, reducing the likelihood of adverse events [85].

7. Conclusion

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To unlock the enormous potential of nanoparticle-based delivery systems, especially for the treatment of cancer, it is essential to deepen the understanding of their benefits and toxicological concerns. Nanoparticles increase therapeutic efficacy and safety by enhancing pharmacokinetic profiles, prolonging the circulation time, improving accumulation in target tissues via the EPR effect, and favouring controlled and sustained release. However, the material composition, surface chemistry, and design characteristics of nanoparticles also influence their acute and chronic toxicity profiles, immunogenicity, accumulation, and long-term fate in the organism. For the informed development of safe pharmaceutical products featuring nanoparticle-based delivery, it is crucial to introduce sound risk assessment and mitigation strategies at the preclinical stage. Existing regulatory frameworks set clear expectations on preclinical and analytical evaluations but also identify a range of materials and formulations that can hardly be addressed by current methodologies. Nanoparticle systems with favourable pharmacokinetic behaviour at the preclinical stage may nonetheless fail during the subsequent clinical evaluation phase. Despite significant progress towards the biomedical application of nanoparticles, many issues remain unsolved and knowledge gaps still hinder the responsible implementation of these delivery systems that promise to reshape medicine.

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Declaration of Competing Interest

The authors say they don't have any known personal or financial relationships or financial interests that could have seemed to affect the work in this study.

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