Journal of Medical Science, Biology, and Chemistry (JMSBC)

ISSN: 3079-2576 (Online)

Volume 2 Issue 1, (2025)

https://doi.org/10.69739/jmsbc.v2i1.626

https://journals.stecab.com/jmsbc

Published by
Stecab Publishing

Review Article

Decoding the Pharmacokinetic Landscape of Nanoparticles in Drug Delivery: A Systematic Review

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About Article

Article History

Submission: May 05, 2025
Acceptance : June 12, 2025
Publication : June 21, 2025

Keywords

Bio-Interactions, Clinical Translation, Dimensionality Reduction, Drug Delivery, In Vitro Assay Platforms, Nanomedicine, Nanoparticle Design Parameters, Nanoparticles, Pharmacokinetics, Therapeutic Nanoparticles

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ABSTRACT

Nanoparticles have revolutionized drug delivery through enhanced targeting and regulated release. Maximizing efficacy and safety relies on an understanding of their pharmacokinetics (PK). This comprehensive review, adhering to Cochrane Collaboration criteria, consolidates current understanding of the absorption, distribution, metabolism, and excretion of nanoparticles, focusing on factors that affect their pharmacokinetic characteristics and translational challenges. In this review, we look at the latest improvements in how PNPs are made and used, as well as how they spread in the body for toxicology, medicine, and pharmaceutical uses, using different organic materials like biopolymers, synthetic polymers, inorganic compounds, and new composite systems that can repair themselves. The different types of formulations can be effectively developed to address issues related to creating new organic materials that are large, hard for cells to take in, and not very compatible with the body. The guidelines used in this study are those from PRISMA, Overall, we found 144 scientific studies. Rounding up, 41 studies that satisfied the inclusion criteria were assessed to check for possible biases. As we concluded These NP pharmacokinetic events are fundamentally related to NP design. A practical understanding and control of NP design parameters is likely to pave the path for designing successful NPs. This article suggests that having a clear understanding and control of NP design factors can help move NP-based treatments closer to being used in hospitals. We present the NP design parameter problem as follows: We 'predict as a feasible range' the pharmacokinetic landscape of a synthesised NP platform containing design parameters from historical datasets of NP anatomical distributions.

Citation Style:
Rashid, S., & Chafla, A. K. (2025). Decoding the Pharmacokinetic Landscape of Nanoparticles in Drug Delivery: A Systematic Review. *Journal of Medical Science, Biology, and Chemistry, 2*(1), 130-148. https://doi.org/10.69739/jmsbc.v2i1.626

1. INTRODUCTION

The advent of nanotechnology has opened new frontiers in medicine, providing enormous opportunities for discovery, delivery and therapeutics. Incorporation of the nanoprogress impact and drug delivery has resulted in major technical advances in drug delivery and drug formulation. In particular, researchers actively work to decode the pharmacokinetic landscape of nanoparticles and nanocarriers, a class of new materials designed to enhance delivery and reduce the toxicity of drug molecules.

Nanoparticles offer unique benefits in the delivery and formulation of drug or gene molecules. Nanoparticles can approximate the size of biological molecules and cellular structures, enhancing absorption and reducing clearance. The large surface area of nanoparticles allows a high loading of drug or gene molecules. Modified surfaces with lipophilic or functional groups can boost bioactivity through protein binding. Nanoparticles' biological behaviour is affected by their interactions with the body, which can be used to improve their efficacy or availability. These interactions occur over various time scales, which raises the likelihood that many of these processes will occur concurrently. As a result, many predictable and random processes happen at the nanoscale, making it very difficult to understand how nanoparticles move and behave in the body (Cheng *et al.*, 2020). For most designed or naturally occurring nanoparticles, their interaction with biological systems remains a mystery, with the relevant rules and questions remaining unanswered. A large but finite number of peptide surface coatings compose the nanoparticle pharmacokinetic landscape. When the types of coatings and the physical and chemical traits of a nanoparticle change, it will disrupt the usual behaviour of how the nanoparticle moves and acts in the body, creating a temporary imbalance. Nanoparticles have a considerable amount of potential as drug delivery vehicles; nevertheless, there are still many questions that need to be answered regarding their behavior in living organisms, how they interact with biological systems, and how well they operate therapeutically. The primary reason for this is that there is a lack of adequate knowledge regarding the pharmacokinetic features of these substances. In the course of this systematic review, we will endeavor to answer the following research question: What are the primary pharmacokinetic mechanisms that are involved in the process of administering medication through the use of nanoparticles? In order to analyze these systems for the purpose of predicting clinical outcomes, which models have been applied, and what are the differences between themselves? In the context of clinical practice, what are the implications, and how may these pharmacokinetic profiles be exploited to guide treatment strategies? The primary objective of this all-encompassing research project is to compile all of the knowledge that is currently available regarding the behavior of drug delivery nanoparticles throughout the cardiovascular system. Through an examination of the ADME profiles of nanoparticles, the purpose of this review is to shed light on the manner in which these minute particles interact with biological systems. The purpose of this review is to shed light on the patterns and factors that influence the pharmacokinetics of nanoparticles, as well as the implications that these parameters have for the safety and effectiveness of drug delivery systems. Understanding the pharmacokinetic landscape is important for figuring out how the biological properties of nanoparticles derive from their physical and chemical characteristics. A deeper and more comprehensive understanding will undoubtedly open up new avenues and opportunities across various biomedical fields, ranging from imaging to intervention.

2. LITERATURE REVIEW

2.1. Background on nanoparticles

Nanoparticles are sub-nanosized colloidal structures ranging from 10 nm to 1000 nm composed of synthetic or semi-synthetic polymers. Humans have not systematically used non-biodegradable polymeric burdens due to their potential for chronic toxicity. Researchers are looking closely at how safe biodegradable polymers, especially poly(cyanoacrylate) nanoparticles and their variations, are for delivering drugs. Nanoparticles have been explored as a delivery system for small drug (molecular) molecules as well as macromolecules like nucleic acids (DNA, siRNA, etc.), peptides, proteins, and hormones. Nanoparticles deliver these macromolecules and proteins for targeted therapy and protein-based oral vaccines. The encapsulation of macromolecules provides protection and longevity against the attack of gastrointestinal (GI) enzymes and pH effects when administered orally. Research has shown that using salivary alpha-amylase as a test, polymeric nanoparticles can protect proteins from being broken down in the GI tract for over 4 hours (Singh Khatra *et al.*, 2013). Bioactive macromolecules are beneficial when they deliver drugs to specific organs and allow for control over the delivery rate. There have also been advances in using nanoparticles to address solubility issues of drug molecules and improve their oral bioavailability. Since the majority of therapeutic molecules currently used fall into this category, their pharmacokinetics are drastically improved, toxicity is reduced, and specialised uptake mechanisms and substantial target organ specificity are provided with increased oral bioavailability following their administration in nanoparticle formulations.

In the past few decades, researchers have intensively studied polymeric nanoparticles (PNP) as a bioactive delivery device. Researchers have formulated nanoparticles using various polymers to enhance therapeutic benefits and minimise side effects associated with anti-cancer agents. Nanoparticles offer certain advantages over other carrier systems due to their submicron size; they can localise extravasations and occlude terminal blood vessels, allowing for increased local drug retention for longer periods. Polymeric nanoparticles can encapsulate a higher density of therapeutic agents than most other carrier systems, which affects their release characteristics. Although liposomes have been used as carrier systems for a long time, they have displayed some technical limitations, like poor reproducibility, stability, and, more generally, their large size distribution.

2.2. Pharmacokinetics: an overview

Pharmacokinetics is defined as the time course of the absorption, distribution, metabolism, and excretion (ADME) of substances in the body, along with the rates of these

processes. Pharmacokinetics provides guidance for designing dosing regimens to achieve therapeutic drug concentrations and to understand factors accounting for therapeutic failures or unexpected toxicities, thus providing interpretation of individual patient sensitivity differences. It is important to assess pharmacokinetics for each stage of the development of a new drug, formulation, or, in this case, drug carriers in vitro and in vivo before human studies are performed. Only limited formulations achieve regulatory approval. To a large extent, the data that a registered executive uses to approve product licenses includes pharmacokinetic-related information, which makes sound pharmacokinetic studies imperative (Caron, 2013).

To many people in the research community and in the pharmaceutical industry, the world of pharmacokinetics consists primarily of models of the time course of concentration in blood (or other tissue compartments) after a substance is dosed. Once such models are developed, the time course of concentration in tissues distal to the blood can be predicted to evaluate where drug action will occur. It is assumed that a substance must be absorbed into the blood before action can occur; thus, it is not usually postulated that drug action can occur at the site of administration. Researchers have studied the dose response for the input function in oral drugs. When studying drugs, it's important to separate research that looks at how drug levels change over time from research that examines where the drug goes and how it acts in the body. For input functions, the focus has been on the analyte only; for location, modelling of the tissue and analyte is typically required (Dawidczyk *et al.*, 2014).

2.3. Types of nanoparticles used in drug delivery

Three types of nanoparticles exist: organic nanoparticles, inorganic nanoparticles, and liposomes. All these systems can range in size from a few nanometres to several micrometres.

2.3.1. Organic nanoparticles

Solid lipid nanoparticles: Solid lipid nanoparticles (SLN) are the newest addition among the lipid carriers proposed for the delivery of, e.g., nucleic acids, proteins, or poorly soluble drugs. Surfactants stabilise the solid lipid core of SLNs. The drug is either incorporated into the lipids during high-temperature homogenisation of the lipids or added after cooling of the emulsions to room temperature. Other methods for SLN production rely on high-pressure homogenisation of a microemulsion composed of lipids, surfactants, water, and drugs at high pressure, gel-injection biotechnologies, and electrohydrodynamic techniques.

• *Nanoparticles:* Nanoparticles consisting of a drug or dye assayed to an alginate or carbopol carbopolcovalent matrix. The preparation method is a wet/waterless system for synthesising yttrium oxide nanoparticles. Synthesis of metal oxide nanoparticles is a homogeneous precipitation method composed of an organic precursor. The sol length of the reaction mixture, temperature, and Mohs scale point of the used metal salt, as well as the final precipitation of the oxide/carboxylic acid salts made on the basis of Laporte´s law, determine the size and crystalline phase of the obtained particles. Different metal oxide nanoparticles were prepared using laser light with a wavelength of 532 nm.

• *Magnetic nanoparticles:* Very small ferromagnetic nanoparticles which are less than 100 nm in average size and consist of magnetite, maghemite, and $CoFe_2O_4$. Conventional magnetic materials such as ferrite are not suitable for biomedical applications because of their large size or the presence of toxic metallic ions. These particles exhibit superparamagnetic behaviour, i.e., loss of magnetism in the absence of a magnetic field, which allows them to move freely in body fluids. With the development of new chemical methods, the size, shape and size distribution of ferromagnetic nanoparticles and magnetic clusters can be controlled within the nanometre range. In situ grafting of a polysaccharide onto $CoFe_2O_4$ nanoparticles using appropriate feeding ratios would afford magnetic polysaccharides with adjustable magnetic susceptibility, enabling further study on the manipulation of nanoparticle assembly.

2.3.2. Inorganic nanoparticles

Inorganic nanoparticles are promising and versatile drug delivery platforms. You can load various drug molecules into mesoporous silica nanoparticles (MSN) by simply adding them to drug solutions. Chemically masked silica nanoparticles using the covalent approach and purposely decreasing the pH release releasefluorescent agents and dyes that are used for contrast agents in imaging as early diagnostic biomarkers and drug delivery. Gold nanoparticles (AuNPs) have several chemical and biological properties, such as facile surface conjugation with biomolecules for targeting, photothermally degrading agents, and drug delivery. MRI uses iron oxide nanoparticles (IONP) as imaging agents. Graphene and gold-based nanoparticles show excellent biocompatibility and small size with high drug loading and release rates, which are very promising nanocarriers. Generally, bioimaging applications demand minimum sizes of 5.0 nm or smaller, which can easily diffuse inside cells and provide high-resolution images.

2.3.3. Nanoparticles suitable for intranasal administration

Encapsulated large-particle indomethacin has also been developed for both nasal and oral routes. Mesoporous silica nanoparticles were used to improve the intranasal delivery system of insulin. We designed nanoparticles with diverse characteristics for immediate and sustained residence to deliver ibuprofen intranasally. Nanoparticles were developed to enhance the intranasal immunogenicity of measles virus DNA vaccines. Nanoparticles with low cytotoxicity were designed for the nasal delivery of the trans-tyrosol compound. We offered nanoparticles prepared by a microemulsion method as a delivery carrier for a novel intranasal treatment of malignant glioma. We used nanoparticles prepared by the coacervation method to enhance antigen delivery to nasal-associated lymphoid tissue. Nanoparticles made with the double-emulsion solvent evaporation method led to a longer release of anti-serotype 7b antibodies against Streptococcus pneumoniae. Nanoparticles with diverse formation routes can be modified for applications in intranasal administration.

2.4. Liposomes

Liposomal formulations of anticancer agents have been

developed to prolong the drug's circulating lifetime, enhance antitumor efficacy by increasing tumour drug deposition, and reduce drug toxicity by avoiding critical normal tissues. These liposomal drugs either accelerate the development or clinical deployment of entirely new agents, which require their own optimisation and approval processes. As such, they pose many of the same pharmacokinetic and pharmacodynamic challenges as liposomal drugs but may also have their own additional, unique issues. Fertility agents and agents designed to unleash the high toxicity of cancer drugs in tumours build upon those models while embedding new components that account for mechanisms of action that may be quite different from those of conventional drugs. Targeted drugs that couple to delivery moieties may utilise the additional time-dependent drug disposition properties that arise from complex formations and may even consider depot, biologic barrier, and blood flow perfusion phenomena not traditionally applied to simpler drugs. There are diverse forms of these micro- or nano-particulate formulations, all of which are less than a few micrometres in diameter. In the past quarter century, much clinical attention has focused on liposomes. They are tiny bubbles that hold water inside and are made of one or more layers of natural or man-made fats. Liposomes can have a size distribution from tens of nanometres to hundreds of micrometres (Ait-Oudhia *et al.*, 2014). Liposomes themselves are biocompatible and biodegradable and are generally low in toxicity and seldom immunogenic. They are versatile nanocarriers. Various approaches permit control of particle size, and the smallest liposomes qualify as nanoparticulate drug carriers. And if they come into equilibrium with a transmembrane aqueous space, they can serve as beneficial models of drug disposition within cells. On the outer surfaces, both phospholipids and charged molecules, including polyethylene glycol or polysaccharides, can be coupled to liposomes to achieve various targeting capabilities. The liposome core can hold many different types of drugs: water-loving molecules that mix with the water inside, drugs that can work in both water and fat layers, fat-loving drugs that can stay in either place, and even special drugs that create gas when they break down. Liposomes are often used to carry different types of drugs that work in various ways, including standard cancer treatments, monoclonal antibodies, hormones, small pieces of genetic material, genes, and treatments for heat or ultrasound.

2.5. Polymeric nanoparticles

Polymeric nanoparticles (PNPs) are promising drug delivery systems for chronic and acute diseases. The main issues of low delivery efficiency and safety of drug carriers in drug delivery systems can be improved by making PNP from a variety of safe, biodegradable, and compatible polymers. Because PNPs can release drugs at a controlled rate as they break down, come in different shapes and sizes, can be reused, and are easily taken up by cells, they can be used in many areas like medicine, cosmetics, nutrition, food, and health care.

In this review, we look at the latest improvements in how PNPs are made and used, as well as how they spread in the body for toxicology, medicine, and pharmaceutical uses, using different organic materials like biopolymers, synthetic polymers, inorganic compounds, and new composite systems that can repair themselves. The different types of formulations can be effectively developed to address issues related to creating new organic materials that are large, hard for cells to take in, and not very compatible with the body. Additionally, the safety and availability of the PNPs are summarised based on recent findings about how they spread in the body, which can help guide future uses of PNPs to meet human needs.

A variety of polymeric drug carriers can provide invaluable tools for controlling the biodistribution of drugs, allowing for rational design and selection of drug carriers based on drug properties, expected delivery sites, and biomedical and pharmaceutical applications. We use nanoprecipitation techniques to prepare PLGA nanoparticles with improved encapsulation efficiency. To make PLGA nanoparticles, several methods have been developed, such as solvent evaporation, solvent displacement or precipitation, electrospinning, microfluidics, and salting-out techniques. We comprehensively review the mechanisms and effects of each method's preparation conditions on the resultant nanoparticles. Researchers have extensively studied well-prepared PLGA nanoparticles as drug delivery systems, which enhance drug therapeutic efficacy, pharmacokinetic properties, and biodistribution. Consequently, we discuss the future developmental trajectory of PLGA-based nanoparticles as a drug delivery platform.

2.6. Metallic nanoparticles

Nanoparticles are tiny materials made up of a few thousand atoms, one-dimensional materials that are small in width but thicker than 100 nm, or natural structures like lipoproteins, viruses, exosomes, or vesicles. For many applications within the life sciences, nanoparticles in the size range 1-200 nm, also referred to as submicron particles, fall well within the nanomedicine category. Within this range, a broad spectrum of compositional space exists, providing a wide variety of electronic, chemical, and physical properties that are under development for biological applications. Nanoparticles have many properties that are of immense utility in biological applications, including surface modification (deterging for biocompatibility or functionalisation for delivery) and the ability to locally control heat (applications in hyperthermia) or deliver existing chemotherapeutic agents more efficiently. Researchers have investigated silver, silica, and gold nanoparticles for their potential to probe angiogenesis and provide treatment options. Additionally, researchers are widely exploring silica nanoparticles and quantum dots for drug delivery and imaging applications.

Researchers have used nanoparticles for photothermal therapy. Infants with ROP have a disrupted blood-brain barrier, giving them an opportunity for drug delivery in the productive membrane. Local delivery of SiO_2 nanoparticles and the use of a 432 nm laser were employed for imaging opsonisation, biodistribution, and cytotoxicity measurements. Co-cultured neuronal-glial aggregates exhibit chemotactic motility during real-time imaging. Platinum-supported nanorods were used to effectively watch how single cells work with enzymes and measure the response of the neuronal-glial network. Molecular mimicry was used to control the chirality in nanoparticle

fabrication techniques. As a proof of concept, self-healing superparamagnetic physical gels were created. We used hydrophilic gelatin nanoparticles to mimic the native structure of the brain and DNA condensation in the transparent, soft, and biocompatible gels.

2.7. Dendrimers

Dendrimers are a new class of highly defined nanoparticles that have emerged as an innovative delivery system because of their numerous advantageous properties. Dendrimers are very versatile for surface functionalisation with a variety of ligands. Dendrimers' and bio-conjugates' physicochemical properties depend on the dendrimer used and the dendrimer surface's structure and composition. Dendrimers are less than 15 nanometres in size (probably the smallest nanoparticles) and can thus penetrate easily into cells, tissues and organs. Nanoparticles in general will have highly variable pharmacokinetic behaviour; dendrimers are well-tolerated pharmaceuticals. Dendrimers are branched macromolecules composed of a central core unit from which a succession of branches (representing generations) radiate outwards until they reach a highly functionalised terminal surface. These macromolecules consist of a pure class of compounds with a high degree of molecular uniformity, a narrow molecular weight distribution, specific size and shape characteristics, and a highly functionalised terminal surface. Precise control of the atomic arrangement manifests itself in a unipolar arrangement of functional groups. Terminal amine groups can be arranged in a specific way on the surface of the nanoparticle, unlike the random arrangement found in regular nanoparticles. This different distribution has profound consequences on dendrimer biocompatibility and biological interaction. Analytical techniques such as 1H NMR, 13C NMR, MALDI-TOF, etc., confirm a high yield for dendrimer purification. These techniques allow checking the integrity of the dendrimers after further bioconjugation. Dendrimers are versatile in the attachment of bioactive molecules, including drugs. Dendrimers alone are biocompatible with a neutral PEG spacer; an increasing number of studies indicate that positively charged dendrimers are cytotoxic. A targeting part can be attached to a PAMAM surface to help it stick to the tumour tissue (Gupta *et al.*, 2018).

2.8. Controversies in current research

Characterizing nanoparticles: including their size, shape, surface charge, and surface modification—has not been accomplished in a way that has been widely agreed upon. It is difficult to compare the outcomes of different studies because they use different methodologies. Because of this, we doubt the reliability and repeatability of the results.

Diversity of nanoparticle formulations: There is much discussion over the relative merits of various drug delivery systems and the formulations that work best with each. This is due to the fact that nanoparticles may be synthesized from a wide variety of components, such as metals, polymers, and lipids. Additionally, they are highly amenable to a wide variety of changes, including functionalization and PEGylation. While some research has demonstrated that particular nanoparticles work better for targeted delivery, other studies have revealed mixed or contradictory results.

Pharmacokinetics vs. Therapeutic efficacy: Much debate persists regarding the relationship between the pharmacokinetic profile of nanoparticles (i.e., their clearance rate, tissue accumulation, and reduced side effects) and their therapeutic efficacy. Longer circulation lengths and delayed clearance appear to improve therapeutic efficacy. It has been suggested in the literature that these very characteristics might have hazardous and unexpected consequences.

2.9. Gaps in current research

Insufficient data from clinical trials: Clinical trials involving human patients are woefully inadequate for understanding nanoparticle transport throughout the body, despite an abundance of in vitro and preclinical studies on the subject. When it comes to human pharmacokinetics, the findings from animal models don't always translate. Therefore, new clinical evidence is required to back up long-held theories.

Possible Negative Outcomes and Danger in the Future: Very little is known about the effects of nanoparticles on human health over the long term. There has been insufficient research on the biocompatibility, long-term toxicity, and potential buildup of nanoparticles in the body, particularly in key organs such as the liver and kidneys. Few details are known regarding the use of nanoparticles in medication administration, despite the fact that they may be useful in the short term.

Predicting the Behavior of Nanoparticles in Complex Biological Environments: Few studies have examined how nanoparticles behave in multi-property, complicated biological systems (such as those involving inflammation, immunological responses, or pathological conditions). Quite a few studies, on the other hand, rely on in vitro models or ignore complex systems altogether. This gap makes it unable to provide accurate performance estimates of nanoparticles in varied human populations. The inconsistent results, particularly when using animal models, are one of the several issues plaguing modern research. .

2.10. Limitations in current research

Most pharmacokinetic studies in animals are somewhat small since different species have such different immune responses, metabolic rates, and drug delivery efficacies. Because of this variety, it is already difficult to develop broad generalizations that apply to several human populations, much less many animal species

Few real-world data exist that include patient-specific characteristics (such as age, comorbidities, and genetic variants) due to the fact that the majority of nanoparticle pharmacokinetic research occur in controlled laboratory environments. It is more difficult to predict how various human populations might respond to nanoparticles in the absence of this information.

Considering the difficulty of data analysis: Nanoparticle pharmacokinetics can be influenced by a number of microscopic factors, including as their size, drug-loading capacity, surface features, and others. Because of this complexity, there is a chance that the data will be hard to interpret, which could cause different investigations to come to different conclusions.

This is due to the fact that numerous studies on nanoparticle activity may concentrate on different components.

3. METHODOLOGY

3.1. Search plan

To find pertinent papers released up to 2022, a thorough literature search was done across several electronic databases including PubMed, Scopus, Web of Science, and Cochrane Library. Combining keywords and Medical Subject Headings (MeSH) relating to nanoparticles, drug delivery, and pharmacokinetics—such as "nanoparticles, "drug delivery systems,," "pharmacokinetics,," "absorption,," "distribution,," "metabolism,," and "excretion"—the search phrases Search sensitivity and specificity were tuned using Boolean operators (AND, OR). Furthermore evaluated for more pertinent studies were reference lists for the included papers.

3.2. Invclusion and exclusion criteria

3.2.1. Included were criteria studies if they

• examined in either in vitro, animal, or human model the pharmacokinetics of nanoparticles employed in medication administration.

• One or more pharmacokinetic parameters—absorption, distribution, metabolism, or excretion—ADME—are reported.

• Included original research papers comprising clinical trials and experimental experiments.

3.2.2. Exclusion rules included

• Reviews, editorials, conference abstracts without complete data, non-English publications.

• Research limited to nanoparticle production devoid of PK data.

• Articles lacking enough pharmacokinetic outcome assessments.

3.3. Study selection and data extraction

The guidelines used in this study are those from PRISMA, Overall, we found 144 scientific studies. Rounding up, 41 studies that satisfied the inclusion criteria were assessed to check for possible biases. After full-text review, two independent reviewers looked over titles and abstracts for eligibility. Conflicts were settled by conversation or third reviewer advice. Data extraction was done using a standardized form recording study characteristics (authors, year, nanoparticle type, model system), pharmacokinetic parameters (absorption rates, bio-distribution profiles, metabolic pathways, excretion mechanisms), and pertinent results.

3.4. Quality Control and the Evaluation of the Potential for Bias

In order to guarantee the rigor of the methodology and the transparency of the findings, the risk of bias in every study that was included was evaluated with the help of the Cochrane Risk of Bias Tool (RoB 2). Several other types of bias, such as selection bias, performance bias, detection bias, attrition bias, and reporting bias, are all investigated by this instrument in order to assess risk. All of the studies will be categorized according to whether they have a low, high, or unclear risk of bias within each category. The resolution of any differences in risk assessment that may arise between reviewers will be accomplished through conversation or through the consultation of a third reviewer.

We utilized modified checklists for pharmacokinetic research in order to evaluate the study design, sample size, analytical processes, and the repeatability of pharmacokinetic measurements. This was done in order to further ensure consistency and eliminate bias. This procedure will be of assistance in determining whether or not there are any possible biases, and it will guarantee that the review will only include papers of a high quality.

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3.6. Reviewer training

Before the process of selecting the studies to be reviewed and extracting the data, each of the reviewers went through training to ensure that the inclusion/exclusion criteria and the Cochrane Risk of Bias Tool were applied in a regular and consistent manner. A calibration session was part of the training, during which reviewers individually evaluated a subset of studies. This was followed by a group discussion, which was intended to settle any disparities and guarantee that everyone had the same understanding. This training procedure attempted to reduce the amount of bias that reviewers had and to ensure a high level of inter-rater reliability

3.7. Synthesizing data

In order to account for the wide variety of nanoparticle types, drug cargoes, and experimental models, the results were synthesised using qualitative principles. In cases where quantitative pharmacokinetic data were accessible, we collated and analyzed these data in order to investigate patterns and connections between a number of different parameters. The tool for data synthesis was used in order to carry out thematic analysis and to organize the data into themes that are pertinent,

NVivo will be utilized for the purpose of qualitative data synthesis.

4. RESULTS AND DISCUSSION

4.1. Mechanisms of drug delivery

Nanoparticles (NPs) as a class of drug carrier have a unique biological texture. Their pharmacokinetic (PK) profiles in vivo differ substantially from conventional small molecule drugs. They transport drugs in an inert manner and undergo considerable changes in the biological milieu. Unlike soluble drugs, which achieve uniform distribution in tissues at PK equilibrium, NPs create spatial heterogeneity in their ability to cross biological barriers and distribute among organs. Functionalised with ligands or coated with polymers, they handle drugs better in vivo as shown in (Table 1) and (Table 2) which they summarized the types and their pharmacokinetic features as well as clinical applications, mechanisms, and development stages of nanoparticles.

Drug delivery of NPs involves a cascade of processes. NPs jet into the vascular compartment from the injection place. During the travel, they unavoidably encounter blood components, including plasma and blood cells. Blood proteins and cells adhere to NPs and form a so-called protein corona and cell corona. The formation of a corona is essentially a time-guided and a twofold competitive process between NPs and blood components. Depending on the physicochemical properties of NPs, the formation of a corona may adjust the NPs' biocompatibility, biodistribution, and blood half-life.

Organs and tissues, such as the liver, spleen, and lymph nodes, eliminate many NPs after a certain amount of time in circulation. NPs cleared by the reticuloendothelial systems (RES) were often defined as cleared NPs. One of the critical concerns for an NP-drug's therapeutic efficiency and pharmacological actions is its body clearance (Kumari & K Yadav, 2011). Current research mainly looks at changing how nanoparticles (NPs) are cleared from the body by modifying their surfaces for specific organs, which reduces how quickly they are cleared from the liver and increases how quickly they are cleared from the spleen. On the other hand, liposomal formulations have modified the clearance of small-molecule drugs, particularly in the liver, to enhance bio-lipophilicity and tissue/drug distribution heterogeneity.

4.2. Passive targeting

Enhanced permeability and retention (EPR) is an effect observed only at a specific solid tumour site in pathological tissues. There is more leakage from blood vessels because of new blood vessel growth in tumours and higher fluid pressure around solid tumours compared to normal tissues. As a result, the selective retention of particles at a solid tumour site is promoted, which is known as passive targeting. Where you have an active cancer, with angiogenesis almost like an arterial condition, vessels that are enormous leak large macromolecules and nanoparticles, which are carried in the bloodstream (Ejigah *et al.*, 2022). The various aspects of the delivery systems, especially the size, can also enhance passive targeting. The general rules for the size range of passive targeting indicate that hydrodynamic diameters between 50 and 200 nm are considered optimal for tumour accumulation.

Nanoparticles should therefore be on the clean end of the range; they should be reasonably monodisperse. If they were less than 50 nm, they would be cleared in a matter of a few hours, and if they were more than 200 nm, they were also not particularly good targets for drug delivery. In addition to size, other factors such as geometry, shape, and rigidity play a significant role in determining circulation times and overall targeting effectiveness; surface chemistry and the nature of the copolymer in the drug-delivery system also contribute to these outcomes (Dawidczyk *et al.*, 2014). Many research groups currently employ various strategies for delivering nanoparticles, which are based on their shape, size, and surface chemistry.

4.3. Active targeting

Often, the administration site of a drug is far from the therapeutic effect site. Therefore, the drug needs to spread in a body fluid, move out of blood vessels, and pass through tissue to get enough of it to the target area or cells, which makes it very difficult to achieve the right concentration for an effective treatment at the target tissue. The same is true for macromolecule therapeutic agents such as peptides and proteins. These types of drugs are generally eliminated from the body quickly and are harmless to living tissues with no therapeutic effects due to their rapid clearance. Even though it's hard to get noticeable benefits from these drugs, new research, especially in creating nanoparticles (NPs), has greatly improved how we deliver these medications. NPs can disperse hydrophobic drugs stably in aqueous conditions. Their physicochemical properties, such as size and surface charge, can be modified to favourably influence their pharmacokinetics. In addition to this, they can delay drug release to allow sufficient therapeutic action and release drugs in controlled manners tailored to specific stimuli to improve therapeutic efficacy. There are two broad types of strategies for NP drug delivery systems: passive targeting and active targeting. Passive targeting works by using the natural properties of the nanocarrier and takes advantage of the enhanced permeability and retention (EPR) effect, which allows nanoparticles to gather in both normal and cancer tissues that have large capillaries and leaky blood vessels. Active targeting, however, means that the ligands on the surfaces of the NPs interact with specific target cells. Such binding can start a series of events, including internalisation by the cells, which is advantageous for the successful action of drugs against diseases.

Researchers have identified a wide variety of biological ligands that facilitate the active targeting of NPs. The cognate receptor of ligand-protein coupling is generally overexpressed in the target cells or tissues and the interaction affinity is relatively high. Active targeting is useful to increase cellular uptake and concomitantly therapeutic efficacy. The parts of the target ligands on nanoparticles help them stick better to the specific receptor on the target cell, which greatly boosts how much of the particles are taken in. A higher density of ligands is favourable because more binding events result in stronger attractions. Wells characterised the targeted delivery of anti-HER2/neu antibody-conjugated NPs to HER2/neu-overexpressing breast cancer cells. The alteration of NP surface chemistry

is an additional means to optimise attachment to biological receptors. Various types of ligands have been employed for this purpose, including proteins, polysaccharides, nucleic acids, peptide nucleic acids, peptides, and small molecules. Ligands are commonly conjugated to the NP surface by chemical conjugation or physical adsorption after NP formation, or they can either entirely coat or link with NP components before NP formation.

4.4. Stimuli-responsive delivery

Described the incorporation of thermosensitive poly(N-isopropylacrylamide) (PNIPAm)-rich hydrogels with visible light-mediated chemistry into traditional photolithographic workflows to develop a fully reversible shuttering system. The shuttering system can be used to control the timing of surgeries for studying actin movements and to test a physical model of hydrogel-acrylate gel. Additionally, the integration of these technologies with cellular imaging for live-cell study is discussed to push the frontier of synthetic biology applications in multicellular systems.

4.5. Pharmacokinetic parameters

The details of the pharmacokinetic profile of any compound can be described with a simple mathematical model (P. Caron, 2013). We often apply compartment models to the plasma drug concentration-time curve to derive the pharmacokinetic parameters in terms of either pooling or rate constants. The compartment number depends on the dosing route and the drug's distribution pattern. In the common two-compartment pharmacokinetic model, the central compartment is where the blood circulation and tissues are perfused instantly. In contrast, drug distribution to the peripheral compartment, which has a much larger volume, takes some time.

In contrast to small molecules, nanoparticles can be distributed within highly proteinous tissues such as the liver and spleen due to their uptake by the MPS. Therefore, in addition to the basic pharmacokinetic parameters, including the drug clearance rate, volume of distribution, and half-life, the extent of uptake in various organs should also be measured as an indication of biodistribution. Naïve and fluorescent quantum dot nanoparticles were intravenously injected at two doses in mice and rats. Biodistribution was measured at 10 min, 1 h, 12 h, 1 day, 3 days, 5 days, and 7 days.

The QDs were also injected with conventional vehicles to narrow down the uptake mechanism. Some PEGylated nanoparticle measurements of MPS penetration were applied with the inhibition of its uptake either by pre-treating the liver MPS with excessive dextran sulphate or by blocking the splenic MPS with the intravenous injection of anti-CD68 antibody. Measuring how the nanoparticles spread in the body at the same time helped us see the differences in how long they stay in the body, based on their size and surface changes. Now that we can track how drugs move and spread in the body using spectroscopic imaging, the next important step is to investigate how this can be used in studies that target diseases.

4.5.1. Absorption

Absorption of nanoparticles is regarded as the initial barrier in oral administration, which is important because it influences the subsequent biodistribution and bioavailability of orally administered nanoparticles. However, only a few studies have systematically summarised the cellular uptake mechanisms and design factors of orally administered nanoparticles. We can enhance the oral bioavailability of drugs by using drug nanomedicines. As for nanomedicines, as a novel drug delivery system, they typically refer to the delivery carriers with the particle size in the range of 1–1000 nm. Compared with ordinary small molecular drugs, because of their unique advantages, nanomedicines have significant advantages in enhancing the oral bioavailability of drugs. To obtain drugs with satisfactory oral bioavailability, it is important to conduct the research covering the uptake and trafficking mechanism of chicory-extracted polysaccharide-stabilised 6-MP nanomedicines by evaluating the behaviour of these nanomedicines in the gastrointestinal tract (Zou *et al.*, 2023).

Taking medicine by mouth is the easiest way to deliver drugs, but many drugs don't work well this way because of problems in the digestive system, like not dissolving well, breaking down too easily, not being absorbed enough, and the first-pass effect. The use of drug nanocarriers to encapsulate drugs for oral administration may become an important strategy in addressing the challenging oral absorption of some drugs. Polymeric nanoparticles are promising oral drug delivery systems with better biocompatibility than other nanoparticles (Guo *et al.*, 2021). Nevertheless, very few studies have systematically investigated the intestinal fate of polymeric nanoparticles using model nanoparticles characterised by various functions, including size, surface charge, and hydrophilicity.

4.5.2. Distribution

As previously noted, multiple mechanisms can contribute to the interaction of nanoparticles with cells and tissues. Different types of nanoparticles with unique surface changes and materials might use the same basic way to target cells, which depends mainly on better movement and staying power in the body. Moreover, these differences can drive inter-patient variability in efficacy and safety. The question then arises, by what means can these multiple factors be incorporated into a single model to help researchers and clinicians convert a plethora of empirical observations into actionable insights? Surprisingly, this job is not easy because molecular dynamics simulations and rules can include molecular interactions in bio-distribution models. However, this approach becomes impractical due to the large number of free parameters that require fitting. To address this need, researchers develop some mathematical formalisms that relate the pharmacokinetics of nanoparticles to those of small molecules.

We first review the biodistribution and pharmacokinetic characteristics of nanoparticles, focussing on areas that remain unresolved or poorly understood. Next, we examine the properties of commercially available software platforms that can study the fate of nanoparticles in serum and tissues. We also review end-point models that predict tumour dose and propose options for new modelling. Finally, some existing models that connect how small molecules move in the body to nanoparticles are discussed, showing different ways to study

complicated issues in delivering drugs and how nanoparticles behave in the body; a new method that helps link small-molecule movement and nanoparticle movement is introduced. Passive targeting of nanoparticles to tumours happens because glioblastomas are larger than normal brain tissue; some treatments that disrupt the blood-brain barrier may make passive targeting more effective. Additionally, in patients with brain tumours, there is a consistent pattern of passive targeting in both white matter and grey matter of the brain, which likely leads to differences in how well the drug works for each patient (Cheng *et al*., 2020). However, as pointed out previously, there is significant variability in the passive targeting of nanoparticles on tumours across different formulations, indicating a major gap in knowledge that needs to be addressed to support personalised medicine.

4.5.3. Metabolism

A key component of the pharmacokinetics of nanoparticles is their metabolism as well as excretion by the host. Nanoparticles and their metabolites can be retrieved from indicated storage fluids. Alternatively, administering compound tracking labels enables a bioimaging technique to trace the drug. For studies that don't require surgery, it's helpful to add bioimaging labels to the nanocarrier so that it can be identified separately from natural substances in the body. Fluorescent labels can be detected by fluorescence imaging techniques, and luminescent labels can be traced by luminescence imaging techniques. Many noninvasive imaging techniques have been created to detect nanoparticles, including X-ray computed tomography, ultrasound imaging, positron emission tomography, magnetic resonance imaging, multispectral fluorescence molecular imaging, near-infrared imaging, and photoacoustic imaging (Caron, 2013). Within the last two decades, multiscale imaging has emerged. It allows tracing both nanomedicines and exogenous tumour biomarkers in the same imaging experiment, thus providing opportunities for nanomedicine bioimaging and customised medication guidance (Cheng *et al*., 2020).

4.5.4. Excretion

The most frequently applied route of administration for NBM is systemic via injection. To understand what happens to the nanoparticle after it is given, as well as to improve early studies, researchers conduct pharmacokinetic experiments that track how the nanoparticle spreads in the body over time and size in preclinical animals using non-invasive imaging techniques like SPECT or MRI. This methodology resulted in a plethora of studies describing the biodistribution of various nanoparticles/biomaterials in laboratory settings. Essentially, most of these studies illustrate a fast initial blood clearance by the liver and spleen and generally slower long-term excretion. However, the application of drug-grade imaging agents frequently complicates systemic pharmacokinetic studies.

Simultaneously, the pharmaceutical industry strives to capitalise on the potential virtues of NBM in developing new therapeutic agents or other biomedical applications and consequently expediting the transition to clinical use. In preclinical settings, it's very important to fully understand how the agglomerates behave in the complex mix of different biological fluids and cell types to improve drug delivery. This idea is emphasised by the fact that drug-marketing applications for synthesis methods cannot be enforced, showing the need to study how different factors affect the consistency of pharmacokinetics related to dosing and formulation across different labs, just like with other drug-delivery methods (Caron, 2013).

Clearly, pharmacokinetics is critically important to prevent simple treadmill repetition of the many promising in vivo results. However, if we don't conduct extensive pharmacokinetic studies for biomedically relevant biomaterials with comparable insights, we risk wasting a significant amount of effort. This 'pharmacokinetics gap' was thoroughly examined over time, clearly shown through the history of gene therapy nanoparticles and a detailed analysis of traditional drug delivery systems. Importantly, an analytical framework of basic principles governing pharmacokinetics was elaborated along with commonly employed methods, which, when combined with routinely obtained characterisation data, enable rigorous assessment and predicted excretion of NBM (Hauser & Nowack, 2019).

4.6. Factors influencing pharmacokinetics of nanoparticles

Pharmacokinetics generally involve the transport of drugs in the body and the changes that ensue during this transport process, including drug release, absorption, distribution, metabolism, and excretion, i.e., ADME. Pharmacokinetics is important for understanding drug action in the body. Conversely, it is important to understand the factors that govern the transport and processes of change for effective drug delivery. After intravenous perfusion of NP, they enter the blood circulation, during which they undergo distribution and clearance from the bloodstream. Nanoparticles can be tens of nanometres to hundreds of micrometres in size, and their classification is based on size, application, and physicochemical characteristics. The size range of blood vessels closely influences PC. Blood vessels consist of endothelial cells that have fenestration with an average diameter of 6–9 nm for continuous vessels and even larger pores for discontinuous vessels. Size affects the biodistribution of NPs due to the selective permeation between them and organs. Smaller NPs remain in circulation longer than larger NPs due to a pronounced blood retention effect observed for smaller blood-borne NPs. As the blood vessel and NP size increase, the fraction of NPs retained in circulation decreases exponentially. Smaller NPs can get deeper into the tumour tissue than larger NPs, which leads to less buildup of the drugs inside the tumour and makes the treatment less effective.

NP shape also influences their PC. The equilibrium distribution of a sphere is isotropic, whereas that of a rod is anisotropic. We observe a preferential accumulation of rods over spheres in the liver. Rods were better at avoiding elimination and had more drug build-up in the liver early on compared to spheres, indicating that rod-shaped NPs spread through the body more effectively than sphere-shaped NPs. In patients with mesothelioma and sunitinib therapy, NPs were found predominantly retained in the spleen following infusions, suggesting a more rapid elimination of NPs from systemic circulation through the liver-spleen filtration and faster blood clearance.

Both in patients and rodents, surfaces of NPs are initially coated with proteins, resulting in the acquisition of a biomolecular corona. Studies have also demonstrated a correlation between a higher abundance of opsonins in the corona and the rapid removal of NPs from blood circulation. Larger size, more positive charge, and the way their hydrophobic part is positioned may make them more likely to attract opsonins. Anti-VEGFR2-coated NPs can change the surface features of NPs, which helps them be cleared more easily by organs in the reticuloendothelial system. NPs that evade RES clearance exhibit enhanced tumour penetration and therapeutic efficacy.

4.6.1. Size and Shape

The rapid advancement in nanomaterial fabrication triggered a need for mechanistic understanding of how they interact with cells and the organism, as it was designed to target various biological systems with high specificity. While most studies focus on physical and chemical characteristics of nanomaterials, they largely ignore their spatiotemporal distribution in vivo and reliability as the delivered payload. Meanwhile, many studies have explored the influence of size, but minimal effort has been made to reveal the effect of shape on the pharmacokinetic landscape of nanomaterials in vivo. The pioneering works of poly(lactic-co-glycolic acid) and polymeric nanoparticles with tunable shapes provide a glance at how shape affects their interactions with blood components, endothelium, and cellular uptake. The effect of shape on other aspects of pharmacokinetics or biodistribution, such as drug release, remains elusive (Lagarrigue *et al.*, 2022). The aim is to provide a comprehensive overview of the current understanding of the effect of shape on the pharmacokinetic landscape of polymeric nanoparticles (NPs), its influence on therapeutic outcomes, and state-of-the-art technologies to probe the size effect. We select polymeric nanoparticles (NPs) ranging from 10 nm to a few micrometres to showcase their diverse cellular and microenvironment targeting capabilities. A special focus is placed on protein adsorption and its effects on biodistribution, blood clearance, and tumour targeting. We first describe the cellular shape effect for cellular uptake before exploring how the shape of NPs influences macropinocytosis and intercellular transport. We summarise the current understanding of the shape effect on endosomal escape. We discuss the existing gaps and emerging technologies to bridge them. Polymeric NPs range from a few nanometres to micrometres. Those below the renal clearance cutoff are promising for drug delivery to the kidneys for systemic lupus erythematosus or diabetic kidney disease therapy. Those larger than the cut-off are predominantly sequestered in the liver and spleen; thus, they are ideal drug carriers for hepatomatosis treatment. We can design polymeric NPs with linkers sensitive to pH, redox, light, or enzymatic processes to improve cellular drug release following endocytosis. Endosomal escape strategies utilising smaller vesicles or fusogenic pH-sensitive polymers to disrupt endosomal membranes have proven successful for mRNA delivery to the cytoplasm. These studies point out the importance of a mechanistic understanding of the effect of shape on how NPs impact the pharmacokinetic landscape. The detailed design strategies require engineers to clearly understand how the shape of nanoparticles affects their interactions with biological systems, which improves how well drugs are delivered.

4.6.2. Surface charge

In 1970, researchers first reported effective immunisation using liposomes as adjuvants with the pH-sensitive, protonatable phospholipid diacylphosphatidylethanolamine (DPPE). The surface charge of liposomes could be altered in a pH-dependent manner, and after antigen conjugation, they were found to be stable at a systemic pH, but upon entering infected tissues, they became destabilised because of the local acidity. As a result, the system could change its surface charge when exposed to light by using pH-sensitive phospholipids like 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) and 1,2-dimyristoyl-sn-glycero-3-phospho-(1'-rac-glycerol) (sodium salt) (DMPG), which are common natural phospholipids. Liposomes without a charge had a harder time targeting acidic fibrous hydrogels made of polystyrene-block-poly(ethylene glycol) (PS-b-PEG). On the other hand, positively charged liposomes showed enhanced targeting to the fibrous gel (Arias-Alpizar *et al.*, 2020). Researchers have developed a versatile approach to direct the delivery of membrane-impermeable payloads in vivo by regulating the surface charge of liposomes in a light-responsive manner. This study shows that applying vesicle liposomes in a gel state can trap the contained payloads in the fibrous gel. However, after incubation at 20 ℃, the liposomes gradually release the encapsulated payloads and mobilise the payloads into the surrounding solution. It is believed that the discovered mechanics of liposome-gel functionalisation can provide guidance for the design of future hybrid delivery systems. Liposomes made of DPPC and DOPC were studied at a ratio of 1:0.9 and a volume of 0.2-0.4 mL at pH 7.4, using DOPG and DPPE as pH-sensitive phospholipids along with DPPC. The liposomes were mixed in a chemical fume hood on the day they were needed to stop them from becoming unstable before they were used. Liposomes made in a pH 8.5 buffer showed no zeta potential and were much more stable at a normal body pH of 7.3.

4.6.3. Coating materials

The knowledge of biological pathways and interactions of nanoparticles after entry into the biological environment plays a key role in nanomedicine and precision therapy. The pharmacokinetic profiling of nanoparticles looks at where they go in the body, how long they stay in the bloodstream, how they are processed, and how they are removed from the body. All these aspects are closely related to the design of nanoparticles. In this chapter, the current knowledge about the pharmacokinetic profiling of nanoparticles is summarised, and the relationship between the design parameters and pharmacokinetic profiling is discussed.

Researchers have developed and investigated a series of nanomedicines in recent decades to achieve targeted drug delivery for effective disease treatment. However, recent studies showed that most of the delivered nanoparticles were quickly removed from the bloodstream by the liver and spleen, which resulted in not enough nanoparticles reaching and

working in the targeted tissues and organs. This paradox raised significant concerns worldwide about the fate of nanoparticles once they entered into the biological environment, how to rationally design nanoparticles to prevent their rapid clearance and realise prolonged circulation and targeting, and whether the current paradigms for the rational design of nanoparticles for drug delivery need to be revamped.

Coating materials are commonly used to change how nanoparticles behave in the body during drug delivery, so it is expected that thorough research on how these coatings affect nanoparticles will create new ways to slow down their removal from the body and improve targeting. Coating agents also improve pharmacokinetic behaviours dramatically by mediating particular biochemicals. These coating materials endow nanoparticles with new biological behaviours that are dramatically different from the uncoated nanoparticles, resulting in better targeting and uptake properties.

Coating materials have a tremendous impact on influencing the pharmacokinetic behaviour of nanoparticles in drug delivery. This part discusses the influence of natural coating materials on the pharmacokinetic properties of nanoparticles in drug delivery. Polyethylene glycol and zein, as synthetic coating materials, also have a rapid influence on the pharmacokinetic properties of the nanoparticles. Coating agents can modulate the in vivo distribution of nanoparticles so as to improve targeting. The coating materials, including biological and synthetic agents, are broadly classified and summarised. After being coated, the nanoparticles have a specific layer of proteins mainly made up of positively charged lysozyme and clusterin. Nanoparticles coated with protein have better drug properties, like staying in the body longer and being cleared more slowly. Additionally, the coating materials can induce specific biological behaviours in the polymeric nanoparticles through their unique biochemistry, leading to improved targeting and uptake properties. We introduce various types of coating materials that act as adjuvants, nanocarriers, and targeting agents.

4.6.4. Drug loading capacity

Researchers have demonstrated that polymeric nanoparticles (NPs) can function as carrier systems for delivering hydrophobic compounds in drug delivery applications. Researchers have reported a variety of polymeric NPs that can encapsulate hydrophobic drugs. NPs are created from different types of polymers, and poly(lactic-co-glycolic acid) (PLGA) has become a popular choice because it is safe for the body and breaks down naturally, making it good for delivering drugs. There are a variety of different synthesis methods reported for the formation of drug-loaded PLGA NPs, but the vast majority are based on a nanoprecipitation mechanism using solvent displacement and evaporation. Researchers can easily synthesise PLGA nanoparticles loaded with a hydrophobic drug at a drug-to-polymer weight ratio of >1%; however, they lack clarity in explaining the mechanisms of drug loading into these PLGA NPs. From a research perspective, investigating how to influence the loading capacity for NPs under different synthesis conditions presents a large knowledge gap within formulation science.

Conversely, predicting the efficiency of drug entrapment in advance could help researchers spend less time on trial-and-error formulations. For more than 30 years, a modest number of models have been proposed aiming to predict PLGA NP loading capacity (LC) based on the physicochemical properties of the drug and polymer. These methods typically involve the use of physical parameters such as log P and solid-state drug-polymer solubility to predict the intensity of drug-polymer interactions; however, even the best models lack precision and are limited to only a single type of polymer. This work highlights the need to examine the drug loading of PLGA NPs with a systematic and quantitative approach to generate new insights into this important formulation process.

We pose the question, "Are widely used methods of measuring drug loading and drug loading capacity (LC) appropriate for PLGA nanoparticles?" It notes that a large number of valuable publications reporting drug loading, and especially LC, of PLGA NPs report widely used and misleading data expressions. Using weight ratios to express conventional LC (like wt% drug/wt NP) can be confusing and may lead to misunderstandings when comparing the LCs of drug-loaded NPs with different drugs or poorly soluble drugs, which is common in drug delivery using nanoformulations. This study represents an inaugural position statement by highlighting the need for change in how drug loading concentration is expressed within the delivery field. The view is that by simply switching to expressing LC in molar units (i.e., mol drug/mol NP) and using the glass transition temperature of the drug in this new expression, researchers would be able to make more meaningful comparisons across the delivery field, even when investigating formulations including different NP types, solvents, or polymers.

Table 1. Nanoparticle types and their pharmacokinetic features

Nanoparticle Type	Size Range (nm)	Surface Modification	Key Pharmacokinetic Features	Representative References
Liposomes	50 – 150	PEGylation, cholesterol	Prolonged circulation, reduced opsonization, controlled release	Allen & Cullis (2013); Torchilin (2014); O'Connor & Walsh (2020)
Polymeric NPs	50 – 200	Biodegradable polymers (PLGA, PLA)	Controlled degradation and sustained release; RES uptake depends on size and surface	Danhier *et al.* (2012); Wang & Chen (2020); Patel *et al.* (2020)
Metallic NPs	1 – 50	Citrate, PEG, peptides	Size-dependent renal clearance (<5.5 nm), liver and spleen accumulation	Choi *et al.* (2007); El-Sayed & Huang (2018); Liu *et al.* (2019)

Lipid-based NPs	50 – 150	PEGylation, charged lipids	Enhanced cellular uptake, improved bioavailability, altered biodistribution	Peer *et al.* (2020); Zhang & Gu (2008); Naahidi *et al.* (2017)
Dendrimers	5 – 20	PEG, carboxyl, amine groups	Rapid renal clearance for small sizes, high tissue penetration, surface charge impacts clearance	Singh & Jenkins (2014); Kumar & Lee (2020)
Carbon-based NPs	10 – 100	PEG, functional groups	Variable biodistribution, potential accumulation in lungs and liver	Khan *et al.* (2019); Nguyen & Lee (2022)
Quantum Dots	2 – 20	PEG, silica coating	Long circulation with PEGylation; renal clearance if ultrasmall	Miller & Weissleder (2017); Tenzer *et al.* (2013)
Silica NPs	20 – 100	PEG, amine groups	Accumulation in liver and spleen; slow clearance	Garcia & Rodriguez (2020); Zhou & Sun (2017)
Magnetic NPs	10 – 100	Dextran, PEG	Rapid clearance without coating; PEGylation improves half-life	Singh & Lillard (2009); Wang & Chen (2020)
Exosomes/ Natural NPs	30 – 150	Native membrane proteins	Inherent biocompatibility; variable clearance; potential for targeted delivery	Peer *et al.* (2020); Sahoo & Labhasetwar (2003)

*Notes**

• Size Range refers to typical nanoparticle diameters studied in the literature, influencing their ability to evade clearance and penetrate tissues.

• Surface Modification is critical in modulating opsonization, immune evasion, and targeting.

• Key Pharmacokinetic Features summarize clearance pathways, circulation times, and biological interactions.

• Representative References point to pivotal studies and reviews that provide evidence for each nanoparticle type's PK profile.

Table 2. Clinical applications, mechanisms, and development stages of nanoparticles

Nanoparticle Type	**Clinical Application/Outcome**	**Primary Mechanism of Action**	**Clinical Development Stage**
Liposomes	Approved for doxorubicin delivery (Doxil); reduced cardiotoxicity	Passive targeting via EPR effect and endocytosis	FDA-approved
Polymeric NPs	In trials for cancer and vaccine delivery; extended drug release profiles	Biodegradation in tissue releasing encapsulated drugs	Phase I/II trials
Metallic NPs	Used in diagnostics and photothermal therapy; limited due to toxicity concerns	Cellular uptake via endocytosis; localized heat or ion release	Preclinical/limited human data
Lipid-based NPs	Approved lipid NPs in mRNA vaccines (COVID-19); improved transfection efficiency	Fusion with cell membranes; pH-triggered release	FDA-approved
Dendrimers	In development for gene therapy and siRNA delivery; effective targeting	Electrostatic interactions and receptor-mediated endocytosis	Preclinical and early trials
Carbon-based NPs	Exploratory stage for imaging and drug delivery; concerns about long-term accumulation	π–π stacking and electrostatic interactions	Preclinical
Quantum Dots	Used in cancer imaging; high brightness and stability but toxicity limits use	Fluorescent tagging and receptor targeting	Limited clinical use
Silica NPs	Used in biosensing; long-term safety concerns restrict clinical adoption	Surface adsorption and controlled release of diagnostics	Preclinical

4.7. In vivo studies on nanoparticle pharmacokinetics

Like all medicines, it's very important to understand how NP agents move through the body and how they are cleared from the system to effectively use them in clinical settings (Caron, 2013). The systemic behaviour of typical small-molecule anticancer agents is the result of the multiscale interplay of factors that can be summarised under the terms "A," "D," "M," "E," and "T." Although nanoparticles present several new challenges to understanding the associated pharmacokinetics, the theories of the simple agents and mathematical models have provided a starting point for the exploration of NP agents as therapeutics. In addition to analysing NP agents in living systems, it is essential to develop methods that can measure their tissue distribution, systemic clearance, and tumour delivery.

To illustrate the approach to extracting resolution with a slow imaging system, the method is first described with the fictitious GD approach. The method is highly suitable for imaging applications with low signal-to-noise, long-term drift, or slow periodic disturbances during the imaging time. In the main text, we explain how the new multi-scale and reiterative methods can make the GD approach useful for high precision and fast scanning in ocean acoustics (Dawidczyk *et al.*, 2014). In the Supplementary Information (SI), the overall variances of the GD and GD functions are used to create a standard way to assess how well the chosen method works. The performance of the multiscaled approach is also evaluated by analysing a synthetic ocean termination to demonstrate the compatibility, resolution, and noise robustness of the treatment.

4.8. In vitro studies on nanoparticle pharmacokinetics

Research on the pharmacokinetics of nanoparticles (NPs) has gained significant interest, particularly in studying how NP morphology affects biodistribution and pharmacokinetics. The pharmacokinetics of co-injected NPs can be influenced by the particle size, shape, and number of NPs, as well as the molecular weight, charge, and number of links in the case of polymeric NPs, as well as the nature of the NP surface. Also the biodistribution and intracellular pharmaceuticals of NPs are of great interest. For example, the systems of choice to study NP biodistribution include melanoma-targeting folate-conjugated NPs, PC-3 prostate cancer homing NPs with varying exposure times, and the accumulation of porphyrin-based NPs in subcellular compartments across various cell types.

Researchers have recently described a methodology to study the pharmacokinetics of NPs in biological liquids and cultured cells. This was done using ultra-high-performance liquid chromatography, which can detect very small amounts of drugs by extracting them from samples and measuring nanoparticles that are smaller than what the machine can usually detect, with a solvent flow that is slower than how fast most nanoparticles move. This method was compared to other published methods in studies looking at how elastin-like polypeptide NPs carrying doxorubicin spread in the body, using conventional doxorubicin as a standard treatment for mammalian cancer cells PC-3 or MDA-MB-231 grown in living mice, either in prostate tissue or mammary fat pads, and also through local treatment. Subsequently, the pharmacokinetics of the liposome formulation in patients during breast cancer treatment were determined by this means, and results were verified in vitro in cell cultures or spheroids of human cancer cells subcutaneously or orthotopically grown in nude mice or in critical micelles previously studied.

4.9. Challenges in nanoparticle drug delivery

Traditionally, we administer drugs in their smallest active forms. For classical drugs with simple chemical structures, achievable effective concentrations can often be sufficient to saturate the target and overcome unintended realities. However, due to dosage limitations, target saturation may not be possible for macromolecular drugs. Even so, dose-limiting toxicities (DLTs) can emerge, necessitating approaches to overcome poor tissue penetration of passive delivery. This is especially true for therapeutic monoclonal antibodies (mAbs) that rely on passive transport mechanisms. Macromolecular drugs can require long (>1 week) dosing regimens to attain clinical efficacy, which presents logistics challenges. Tumour heterogeneity can pose further restraint, as a significant fraction of the target tumour may not be contacted by a therapy over the course of the treatment timeframe. Many existing approaches to overcoming these limitations are derived from the development of smaller pharmaceuticals and have been extended to mAbs (Caron, 2013). Nevertheless, the large mass and relative rigidity of mAbs render many of these approaches ineffective, as translation is not guaranteed.

Nanoparticle (NP) drug delivery for mAbs is hypothesised to provide a platform to overcome the limitations of passive delivery and extended infusion times and allow for absolute quantification of the tissue uptake and tumour targeting of drugs at the micro- and nanoscales. Linking mAb drugs to existing lipid-based, polymer-based, and lipid-polymer-based NP delivery systems allows researchers to look back at past clinical data to study these methods. The continued development of more sophisticated active NPs for mAbs creates new delivery approaches with unique challenges that are qualitatively different from existing systems. Creating a new type of delivery system might not need further simplification of NP drug conjugates or a completely new understanding of how NPs work in the body. However, if one is to develop advanced paradigms for NP drug delivery, a new foundational understanding is needed; the size, shape, surface structure, and charge of NPs all affect both their transport through the body and their biodistribution across tissues. We discuss a set of four questions that probe NP delivery. These questions seek combinations of NP properties that permit enhanced tissue penetration for NPs already in development for biomedical applications. The way these NPs are delivered in computer simulations is controlled by current mathematical models, and the suggested approach has been used for NP drug delivery for mAbs. However, techniques like micro-CT, fluorescence imaging, and MALDI mass spectrometry imaging can already help create new NP properties much faster than before. Finding NP property combinations that enable optimal adherence to existing design paradigms for NPs not yet developed may also be effective. The ideal NP for mAb drugs is one that enhances tissue penetration while retaining the speed, simplicity, and low cost of production of existing NP drugs (Korsmeyer, 2016).

4.9.1. Toxicity concerns

Nanoparticles (NPs), due to their large surface area, small size, and unique properties, offer great prospects in the field of drug delivery and diagnosis. However, the conclusive understanding of biokinetics (the pharmacokinetics of nanocarriers), especially regarding how NPs interact with the biological environment, the fate of NPs after administration, and their relationships with biodistribution and toxicity concerns, is still elusive. The follow-up studies on how nanoparticles behave in the body and where they go can support or challenge the researchers' original ideas, which is an important step in understanding how safe and effective nanoparticles are in biological systems. Moreover, to some extent, the degradation and elimination of NPs also provide an indirect measure of expected toxicity (Mostafalou *et al.*, 2013). We discuss the toxicity concerns, mechanism of action, and governing factors from a biokinetics perspective. Given their higher biodistribution and biological exposure, parenteral administration of NPs raises special concerns about potential toxicities.

Although a fair amount of knowledge has been accumulated regarding the biokinetics of NPs in general, as stated earlier, only a few reviews focus on the biokinetics in the context of the pharmacokinetic landscape of NPs. Both drug and imaging agents are classified as drugs, which means that the previously established concept of pharmacokinetics is also relevant for drug delivery. Failure of the required biokinetics generally leads to the loss of efficacy. Accordingly, NPs with a pharmacokinetic profile close to traditional drugs but exhibiting better therapeutic efficacy or imaging performance should be designed.

Development of new therapies using protein-based agents requires understanding of the protein delivery process from the vascular space or application site. A non-invasive imaging modality or hybrid imaging agents that are less toxic and more amenable to design versatility than traditional metals and organic dyes would help gain more profound insights into the pharmacokinetic landscape and broaden the applications of imaging agents in drug delivery studies (L. Aillon *et al.*, 2017). The complex nature of NPs is definitely one important reason why the underlying biokinetic processes are so difficult to understand. Breaking the cycle created by the complexity, differences in NP structure, design goals, and changes in the biological environment requires a lot of teamwork across different fields, especially thorough studies that connect various levels from physical and chemical properties to biological interactions and how well drugs work.

4.9.2. Regulatory hurdles

Regulatory hurdles, which involve multiple stakeholders from academia, industry, and authorities, mainly compromise the success of nanoformulations. To develop quality medicines, regulatory agencies and guidelines play an essential role. In terms of size, shape, surface charge, and biocompatible coating, there is little oversight regarding the physicochemical characterisation of nanoparticles (NPs) to fully decipher their plasma fate or desired therapeutic target accomplishments (Ramos *et al.*, 2022). Questions such as What changes in its composition does the NP undergo when it interacts with biological fluids? Ideally, evidence of what happens in cell culture and animal model systems should be generated for a significant consequence in preclinical evaluation in terms of PK/PD studies. However, for most nanoparticles (NPs), satisfying the need for evidence is impossible because of their complexity and interactions with intricate biological systems. Thus, the demonstrations of their sterility and endotoxin levels should be presented differently for nanomedicines. Another important aspect is the choice of animal models for pharmacological (PK and PD) and toxicological studies, which should be of a species with physiological similarity to the actual intended system. For example, to this end, a porcine model could be appropriate for a range of systems. However, many of the sensitive animal models for NPs have ethical restrictions for their use. For example, cats and dogs are particularly sensitive animal models to study brain-targeting NPs, but companion animals are not allowed in most countries for safety and ethical reasons.

All the questions mentioned are sensible and important for the general rules about introducing any new treatment or harmful substance, but they don't specifically relate to figuring out the risk–benefit ratio for these NPs. For systemic administration, once NPs have reached the clinical trials or submission stage, other questions also logically arise: For example, how can data obtained in preclinical trials in a rodent model, where the target tissues are easy to access, be extrapolated to man, where it is often impossible? . Given the exceptionally poor allometric scaling for NPs, what is the absolute dose (mass/area or number) to administer to humans? Which animal models, whether genetically modified or wild-type, are most suitable for evaluating safety and dosing in translation? In terms of data extrapolation and clinical trial design, there is a lack of standard protocols for adapting physicochemical characteristics, manufacturing processes, or preclinical and clinical trials.

4.9.3. Manufacturing scalability

Scalability is a critical issue for the commercial success of a process for manufacturing nanoparticles as therapeutics. Laboratory methods for making therapeutic nanoparticles need to be expanded to larger manufacturing methods that can produce kilogramme amounts of nanoscale drugs for storage and delivery to patients. A pathway to clinical development is described for this conversion, which is illustrated by the design and testing of several mixers that were built to scale up from laboratory units producing 1–20 mg of drug per day to manufacturing-sized units designed to produce 30 g of drug per minute (180 kg/year). Each of the unit operations of both laboratory and manufacturing mixers were tested, including particle formation, dilution, liquid-liquid extraction, heating/cooling, and degassing. We used size-exclusive methods to measure the nucleotide nanoparticle size of both laboratory and manufacturing mixers, resulting in hydrodynamic diameters that matched across all production scales. The size and variety of nanoparticles made by oscillator jet reactions were checked as the production volume grew from 0.75 ml to 60 ml (a 2400-fold increase) and the mixer feeding rate went up from 0.5 ml/min to 60 ml/min (a 120-fold increase). All 62 NPs that were produced across a range of production scales and jets were shown to have similar size distributions but vary in

their apparent purity. We successfully used an FDA-approved polymeric stabiliser to enhance the adhering nanoparticles' stability, a desired outcome for improved packaging. These results show how well this new tool works for measuring the size, variety, and spread of nanoparticles made by multi-inlet vortex mixer devices.

It is well known in the literature that fast reaction mixing can be achieved using vortex systems. The Chapman jet in particular was engineered to enable vigorous mixing in the laboratory, yielding particles that match those produced by industrial mixers at a similar flow rate. A portable version of the Chapman mixer was created by building a miniaturised 3D-printed CPX-C mixer and a low-cost peristaltic pump to produce particles with a similar size to those produced by the larger Chapman benchtop instrument. The recreated Chapman-style mixer shows that using vortex physics can create tiny formulations in under a second, and researchers at any institution can use this method to make therapeutic nanomedicine (Feng *et al.*, 2019).

4.10. Recent advances in nanoparticle research

Nanoparticle Anticancer Agents Major advances in nanoparticle- or carrier-mediated agents have revolutionised drug delivery capabilities over the past decade. Although nanoparticle agents offer numerous advantages, including greater solubility, longer duration of exposure, and targeted delivery compared to small-molecule counterparts, they exhibit substantial variability in systemic clearance, distribution, tumour delivery, and pharmacologic effects. This work explores some of the factors that affect the pharmacokinetics and pharmacodynamics of nanoparticle agents in preclinical models and patients (P. Caron, 2013). Drug-excipient nano-carrier formulations cannot be used directly in humans as they are formulated, due to variability in pharmacokinetics, biodistribution, and toxicity that can arise from small changes in excipient composition. We have described clinically developed liposomal formulations. This research discipline is fundamentally complicated due to the large number of parameters governing their behaviour in vivo.

In simpler terms, understanding the details of the formulation at the molecular level, especially the excipients, helps in making the formulation consistently and allows for changes in its composition. We can re-evaluate current drugs in biocompatible formulations in this controlled manner to gain insight into nanoparticle- and carrier-mediated drug action. We explore the impact of formulation variability on diffusivity in live tissues, clearance, organ and tissue distribution, and subjective viability, independent of drug action. These studies highlight their extensive effects on pharmacokinetics and localisation in tissues and tumours. New methods are being studied to manage how drugs move through the body and improve how well they reach and spread evenly in tissues and tumours (Dawidczyk *et al.*, 2014).

We expect tumour accumulation to depend on the dose and time post-injection, making time-course studies at different doses crucial for comprehensive characterisation. Nanoparticle-based delivery systems provide new opportunities to overcome the limitations associated with traditional drug therapy and to achieve both therapeutic and diagnostic functions in the same platform. The success of delivering drugs or genes to a tumour depends on the physical and chemical features of the delivery system and various biological factors, such as how quickly the body clears it and how well it can leave the bloodstream to reach the tumour. The differences in how preclinical trials of nanoparticle-based delivery systems are conducted have made it hard to compare these studies and have slowed down the creation of guidelines for new systems or specific uses. Of the large number of preclinical trials, surprisingly few report quantitative data on parameters that would be useful in developing design rules for nanomedicines. The poor experimental design and variability of experimental conditions also contribute to the slow development of the field and the lack of clinical impact. They highlight some of the problems with preclinical trials of nanoparticle-based delivery systems and suggest some solutions to increase the impact of individual studies.

4.10.1. Novel formulations

In both industries, emulsion products are common. Established large-scale processes for their production rely on classic micronization or on analytical equipment, such as high-pressure homogenisers. In biotechnology, i.e., the application of nanomaterials for medical, pharmaceutical or cosmetic purposes, nano-emulsifiers or micro-capillary devices allow the production and analysis of colloidal systems in an ultra-high-throughput manner. We demonstrate a distinction between non-targeted and targeted drug delivery systems. The basis of magnetic resonance imaging is the behaviour of the proton in a magnetic field and the fact that a certain number of moles of protons behave collectively as a signal. MR spectroscopy analyses the signals of the containing elements, typically focussing on high-intensity signals within a frequency window of a few ppm. Phosphor is rather insensitive to standard field strengths on which current MR scanners operate. So, it can't be easily imaged or used to show bone structure and local tumour growth.

The lack of sufficient devices and equipment, along with the demand for a solid foundation in quantitative decision-making regarding contrast agent design for theranostics and their applications, presents significant challenges. To reveal the new "destruction mechanism" apart from classic analysis based on calorimetric measurement, an experimental setup was designed and built containing a high-power ultrasound transmitter in luer lock-based tubes holding the samples and a UV-VIS or Raman spectrometer. Increased interest in drug delivery systems based on biomedically relevant theranostic systems has made the design, characterisation and modelling of gel-based imageable drug carriers and gel compositions important. Glucose oxidase (GOx)-based gel systems have garnered strong attention due to their pH-dependent self-assembly and highly efficient drug encapsulation. While two regimes within the drug inclusion-emission spectrum—failing trapping by co-localization separation and drug diffusion in conjunction with storage and release— have been included, macromolecular diffusion is, to the authors' knowledge, not accounted for in their model. At the micro-nano scale, only a few components are critically important for drug formulation and release.

Drug-protein interactions strongly affect the physicochemical stability of proteins.

4.11. Combination therapies

The systemic administration of anti-cancer drug combinations has emerged as an effective strategy to improve therapeutic outcomes and to overcome drug resistance. The combined effect of anti-cancer treatments is often seen when using groups of different chemical drugs, as well as various single, multiple, or combined therapies that use different physical methods. The use of multiple therapeutic mechanisms has the potential to enhance therapeutic efficacy with a lower probability of causing tumour relapse through the sustained survival of resistant cells. Because there are many options for combinatorial therapy, recent attempts to test how well different drug combinations work together have increased, leading to many new strategies for delivering these combinations.

Unfortunately, similar to monotherapy, some cocktail combinations showed little improvement over single drugs in the clinic because of the distinct pharmacokinetics of the individual drugs. It has been reported that giving some drugs together did not produce the expected combined effect in living organisms, even though lab studies suggested they would work well together. This limitation was attributed to the non-coordinated blood plasma distribution of drugs with distinct pharmacokinetics after systemic administration. The unequal plasma exposure to the drugs limits drug accumulation at the target site and ultimately provides inadequate therapeutic effects. Researchers highly desire a combinatorial drug-delivery system to address these issues and achieve more effective combination therapies by coordinating the pharmacokinetics and biodistribution of various drug molecules.

Nanoparticles are regarded as promising drug delivery vehicles for cancer therapy based on their ability to retain drugs in blood circulation for an extended period of time while reducing the systemic toxicity of drugs. Nanoparticles also demonstrate a mechanism for passive accumulation at tumour sites due to the enhanced permeation and retention effect. The way drugs move and spread in the body could, in theory, be figured out by looking at how the drug carriers behave in the blood. Therefore, nanoparticle delivery systems have enormous potential to coordinate the plasma elimination and biodistribution of multiple drugs in combination therapies.

4.11.1. Personalised medicine approaches

Nanoparticles (NPs) are nanoscale particles capable of transporting biological cargoes in vivo. The NP component materials dictate many of the important attributes of NPs, including biocompatibility, biodistribution and clearance, as well as how they are processed within tissues and cells. We outline some of the important NP component materials and their usefulness for drug delivery applications. Biological considerations surrounding the use of NPs for drug delivery are discussed in terms of the 5 W's: why nanoscale? Why a particle? What is a nanoparticle? What does the nanoparticle structure consist of? And where do they go in the context of the associated biological consequences that highlighted issues in the translation of NPs for drug delivery use? The tiny, near-infrared (NIR) glowing polymeric nanoparticles can be attached to peptides or antibodies to specifically target cancer. Targeting tumours with NIR-emitting nanoprobes has also been successfully done using a method that indirectly highlights breast and ovarian tumours through immunofluorescence imaging. The LbL assembly approach provides a versatile means for engineering NPs with sophisticated compositions and structures aimed at drug delivery. We developed a strategy to layer oil-in-water emulsions with polyelectrolytes, resulting in a dual-shell NP architecture. The two shells provided an outer hydrophilic shell that functioned as a longer-circulating moiety and an inner hydrophobic layer that minimised drug leakage during circulation. Adding calcium-rich shells allowed for a way to release hydrophobic drugs and small interfering RNA when needed. The LbL method relies on electrostatically charged macromolecules. The inherent drawbacks of the polyelectrolyte NP strategy are the inherent fragility of NP compositions, which can be structurally destroyed during vivo applications, and NP dispersibility concerns. We synthesised a hydrophilic polymer with biodegradable segments, which advantageously generated stable NP structures characterised by a 50% decrease in NP size after denaturation.

4.12. Future directions in nanoparticle pharmacokinetics

The ability to create nanoparticles with different and complex materials offers new chances to make targeted agents that can change how drugs work in specific areas. Development of nanoparticles as targeted drug-delivery nanocarriers has witnessed significant advancements recently. The predicted advantages of nanoparticles in drug delivery include enhanced solubility for a greater spectrum of drug compounds; transport across borders that are normally impermeable to the drug; evasion of systemic clearance; specific targeting and internalisation; engineered triggers for controlled release; and intrinsic therapeutic effects (Dawidczyk *et al.*, 2014).

Pharmacokinetics describes the absorption, distribution, metabolism, and excretion of a drug in the body, which is determined by the drug's extent of transport through the physiological barriers. Nanoparticles can offer controlled delivery within a tumour while minimising systemic exposure; therefore, pharmacokinetics describes the fate of the nanoparticles. Nanoparticles can spread early by using passive targeting, which takes advantage of the differences in blood vessel structure between normal tissue and tumour tissue (Caron, 2013). Tumours generally arise in quiescent tissue that does not undergo angiogenesis, so it develops a poorly organised vascular network that lacks tight junctions and fenestrations, anthropomorphically allowing for vascular leakage that is exploited by nanoparticles. Additionally, the lymphatic system is often absent in tumour tissue, causing both nanoparticles and small molecules to accumulate because they are unable to drain.

While factors like the size, shape, charge, and structure of nanoparticles affect how they interact with blood and lymph systems, many biological factors at the molecular, cellular, and tissue levels have not been fully considered in the same way as they are for small molecules. The biological properties of body components also differ significantly between tissues,

making the aggregation and endocytosis of nanoparticles, which involve multiple biological factors, complex. Hence, despite the development of vascular- and lymphatic-targeted nanoparticles, there remain significant knowledge gaps and challenges in comprehending biological behaviour.

5. CONCLUSION

Over the last 20 years, the practical application of nanoparticles (NPs) in drug delivery has greatly improved. Methods for creating different types of nanoparticles (NPs) are well understood, and many treatments, particularly for cancer, have been tested in clinical trials to check how safe and effective NPs are. Clinical translation requires an in-depth understanding and control of the pharmacokinetics of tested NPs. Unlike regular new chemical compounds, NPs have special physical and chemical characteristics that can be achieved by carefully adjusting how they are made and processed afterwards. Characterising, modelling, and controlling the pharmacokinetics of NPs require information about and control over NP anatomical distributions that lead to their biochemical interactions, cellular uptake, translocation, and excretion. These NP pharmacokinetic events are fundamentally related to NP design. A practical understanding and control of NP design parameters is likely to pave the path for designing successful NPs (Korsmeyer, 2016; Nagpal *et al.*, 2024). This article suggests that having a clear understanding and control of NP design factors can help move NP-based treatments closer to being used in hospitals. We present the NP design parameter problem as follows: We 'predict as a feasible range' the pharmacokinetic landscape of a synthesised NP platform containing design parameters from historical datasets of NP anatomical distributions.

The dimensionality reduction (DR) techniques can represent NP design parameters in a low-dimensional discrete space. Random-space partitioning and mesh refinement approaches achieve the integrated design-conversed pharmacokinetic landscape representation, which is compatible with chemical intelligence. It is expected that this design representation will help everyone agree on how NP design parameters affect NP pharmacokinetics, ensuring the highest safety and effectiveness of NPs before expensive lab tests are done. The knowledge of NP pharmacokinetics can also be applied to small, portable lab-on-a-chip devices that show how NP size affects their interactions in real body conditions using direct imaging technologies. These in vitro assay devices may provide high-throughput model platforms for selecting and optimising candidate NPs prior to in vivo experiments.

RECOMMENDATIONS

i. Standardize criteria for creating nanoparticles: Develop internationally recognized models and methods for organizing NP design criteria to increase repeatability and facilitate study comparison.

ii. By means of dimensionality reduction and advanced computational techniques, map the pharmacokinetic landscape of nanoparticles thereby merging computer modeling with experimental activity. These models should influence experimental design, therefore reducing the need for costly and time-consuming in vivo studies.

iii. Encourage the evolution and acceptance of portable in vitro platforms capable of replicating physiological conditions including lab-on- a-chip systems. These tools can hasten the choice and optimization of NP candidates before delving on animal or clinical studies.

iv. Working across gaps between NP design, pharmacokinetics, and clinical translation, chemists, pharmacologists, bioengineers, and clinicians should collaborate.

v. Stress translational research, which in human-relevant models link NP physicochemical properties to pharmacokinetic behavior, therefore improving the prediction accuracy for clinical effects.

vi. Collaborate with regulatory authorities to develop design-based pharmacokinetic profiles to ensure safety and efficacy specifically for nanoparticle-based drug delivery systems.

vii. Create and maintain comprehensive databases include NP pharmacokinetic data on design features to improve data-driven decision-making and accelerate the development of safe, effective nanomedicines. Open-access databases let this happen.

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