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A Machine-Generated Literature Overview

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Preface

The science of drug delivery has witnessed remarkable advancements in the ever-evolving era of pharmaceuticals and healthcare that promise to revolutionize clinical therapeutics. Among these breakthroughs, nanoparticles and novel drug delivery systems (NDDS) have emerged as game-changers, offering enhanced drug efficacy, reduced side effects, and improved patient outcomes. This book, *Pharmacokinetics and Pharmacodynamics of Novel Drug Delivery Systems: From Basic Concepts to Applications*, delves deep into the intricate world of these cutting-edge technologies. It seeks to unravel the mysteries of how nanoparticles interact with the human body, the dynamics of drug release, and the impact of these innovations on therapeutic response and clinical outcomes.

Nanoparticles represent a promising frontier in pharmaceuticals. Their ability to transport, protect, and release drugs with precision is nothing short of astounding. The intricate interplay between nanoparticles and biological systems, the optimization of drug loading and release kinetics, and the quest for enhanced therapeutic efficacy demand a comprehensive understanding. Beyond nanoparticles, novel drug delivery systems encompass a wide array of ingenious techniques and formulations. From liposomes to microneedles, from implants to inhalation systems, each chapter explores the unique characteristics, challenges, and opportunities associated with these innovative approaches to drug delivery.

This book is an effort to provide a comprehensive understanding of the nuances of NDDS and its impact on the fascinating science of PK & PD. Each chapter is a carefully crafted exploration of a specific aspect of nanoparticle-based drug delivery or a novel delivery system, offering a holistic view of the subject.

The book is intended for researchers, clinicians, students, and anyone with an interest in the future of drug delivery. Whether you are a research scientist looking to strengthen your understanding or a student embarking on a journey of discovery, this book offers something for everyone. It is our hope that this book will serve as a beacon, guiding you through the complexities and possibilities of this field. As you embark on this voyage, we invite you to explore, question, and envision the future of pharmaceuticals with us.

Welcome to the world of *Pharmacokinetics and Pharmacodynamics of Nanoparticles and Novel Drug Delivery Systems*.

Munira M. Momin

Disclaimer

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Please note that the selected papers are not used to train an LLM while the auto-summaries are created.

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About the Editors

Sankalp A. Gharat Prof. Sankalp Gharat is presently working as an assistant professor in the Department of Pharmaceutics at SVKM's Dr. Bhanuben Nanavati College of Pharmacy (BNCP), Mumbai, India. He has earlier served as assistant professor in the Department of Pharmaceutics (2018–2019) at Humera Khan College of Pharmacy, Mumbai, India. Before joining academics, he was associated with Macleods Pharmaceuticals R&D Centre, as a research scientist in the formulation and development of topical (ANDA) conventional and novel products in the Dermatological Section for regulated market (US and EU market). He has worked as a research associate fellow (2014–2016) in research project on cancer management sponsored by the University of Mumbai. His research interests include formulation development of novel drug delivery and targeted systems based on nanotechnology for cancer, rheumatoid arthritis, psoriasis, and ophthalmic use. In his area of research, he has several national and international papers published in peer-reviewed journals in collaboration with Laurentian University, Bhabha Atomic Research Centre, and Ajman University of United Arab Emirates. He has been awarded with title "SPDS India Young Researcher 2024" by Society for Pharmaceutical Dissolution Science (SPDS) and "Promising Young Faculty Award 2023" by SVKM's Dr. BNCP. He has secured first place for two consecutive years at the prestigious 15th and 16th AVISHKAR Research Convention—University of Mumbai, in Medicine and Pharmacy Category (2020–2021 and 2021–2022). Prof. Sankalp is a recipient of "AICTE Scholarship for

2014–2016" and "Meyer Organic Academic Excellence Award 2016" by Meyer Organics Pvt Ltd for his academic performance in bachelor's program. He has delivered several research talks and interacted with students of various pharmaceutical institutions. He is actively involved in training students for conducting cell culture-based experiments for toxicity testing of formulations and phytochemicals. He is a member of professional societies like the Association of Pharmaceutical Teachers of India (APTI) and Controlled Release Society (CRS-Indian Chapter).

Munira M. Momin Prof. Munira Momin is a professor and principal of SVKM's Dr. Bhanuben Nanavati College of Pharmacy, Mumbai, India. She has earlier served as professor in the Department of Pharmaceutics (2012–2015) at Oriental College of Pharmacy, Navi Mumbai, India, as associate professor (2005–2011) at LJ Institute of Pharmacy, Ahmedabad, India, and as assistant professor (2003–2005) at LM College of Pharmacy, Ahmedabad, and SK Patel College of Pharmaceutical Education and Research, Mehsana, India. Her research interest is in targeted drug delivery and bioengineered polymeric nanoparticles with a specialization in brain-targeted nanosystems. She has been conferred with prestigious Nehru-Fulbright Academic Excellence in Higher Education seminar for the year 2019. She is a recipient of topmost influential principal award (pharmacy category) for the year 2022 for her contribution in administration and research and bringing positive changes among students by setting up social sensitivity cell at her institute. Dr. Momin is a recipient of ACG-Best Research Paper Award of IDMA during the year 2020–2021 and ML Khurana Memorial Best Research Paper Award by IPA for the papers published during 2008–2009. She also has FH Jani Gold Medal for securing first merit during BPharm program. She has published more than 80 scientific articles in peer-reviewed international journals and authored or co-authored numerous books and book chapters. She has five granted Indian patents to her credit. She is a member of many professional societies, i.e., Indian Pharmaceutical Association (IPA), Association of Pharmaceutical Teachers of India (APTI), Society for Pharmaceutical Dissolution Science (SPDS), and Controlled Release society (CRS-Indian Chapter). She is a scientific chair of Disso-India, an annual conference arranged by SPDS.

Tabassum Khan Dr. Tabassum Khan is Professor, Department of Pharmaceutical Chemistry and Quality Assurance at SVKM's Dr. Bhanuben Nanavati College of Pharmacy, Mumbai, India. She is a recipient of the prestigious Erasmus+ Teaching Mobility Fellowship, ERASMUS Foundation, European Union Programme 2023; Shastri Indo-Canadian Institute, Shastri Mobility Programme Fellowship Award 2018; P.D. Sethi National Award for Best Research Paper on HPTLC, 2017, and the Indian Pharmaceutical Association B. Pharm Merit Award, 1990. She is on the reviewer board for science fund of the Republic of Serbia, 2023 and 2021; National Science Centre Poland, 2022; New Frontier Seed Grant Program, Network for Canadian Oral Health Research, Nova Scotia, Canada, November 2019 and 2018; Shastri Indo Canadian Institute, MHRD, India, under the Collaborative Research Category, October 2019; and Medical Research Council, UK, under the South Africa (Newton)–UK Antibiotic Accelerator 2019 program, 2019. Her thrust areas of research include medicinal chemistry, natural product chemistry, and nanotechnology-based drug development. She has 2 Indian patents, 78 publications, and 8 book chapters to her credit. She is life member of the Indian Pharmaceutical Association and Society of Pharmaceutical Education and Research and member of the International Federation of Pharmacists and American Association of Pharmaceutical Scientists.

Chapter 1
Introduction to Pharmacokinetics and Pharmacodynamic Studies of Novel Drug Delivery Systems

Sankalp A. Gharat, Munira M. Momin, and Tabassum Khan

1.1 Introduction

Nanoformulations have evolved to circumvent the limitations of conventional drug delivery systems. Novel Drug Delivery Systems (NDDS) have emerged as innovative approaches that enhance the efficacy and safety of drug therapies. NDDS includes a diverse range of nanotechnologies designed to optimize the delivery of therapeutic agents to their intended targets within the body. The need for nanoformulations arises from the limitations of traditional drug administration methods, that often results in suboptimal therapeutic outcomes and reduced patient compliance [1]. The history of NDDS is an interesting narrative of human ingenuity and scientific progress; the first controlled-release polymer device was developed in 1964. Bangham discovered the liposome in 1965; albumin-based nanoparticles were reported in 1972; liposome-based formulations were developed in 1973; the first micelle was developed and approved in 1983; the USFDA approved the first controlled formulation in 1989; and the first polyethylene glycol (PEG)-protein conjugate hit the market in 1990 [2].

The term "NDDS" covers various macro-micro-nano strategies and platforms that modulate the formulation for release, and targeting of drugs. These systems are designed to specific disease states, and patient populations, offering personalized

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and optimized treatment approaches. Drug products containing nanomaterials possess distinct characteristics due to potential alteration of their chemical, physical, or biological properties in comparison to conventional pharmaceuticals, significantly impacting the quality, safety, and effectiveness of the product [3]. Nanomaterial-based drug formulations may exhibit a different pharmacokinetic profile as compared to traditional formulations containing the same drug. Once a drug loaded nanoparticle enters the bloodstream, it has the capacity to engage with specialized immune cells known as macrophages. These macrophages engulf the nanoparticles and facilitate its targeted delivery to specific locations that are typically challenging to access for conventional formulations [4]. In another scenario, a pharmaceutical formulated as a nanomaterial incorporates a unique "shielding" mechanism designed to prevent interactions with immune cells, enabling the drug to circulate in the bloodstream for extended periods, ultimately reaching its intended destination, such as tumor tissues. This capability to selectively target specific areas while avoiding others substantially reduces the risk of side effects and off-target toxicity, resulting in enhanced therapeutic efficacy [5–7].

Nanomaterials find their primary application in the treatment of conditions like cancer and microbial infections [8–10]. However, it is a challenging process to comprehend the transit of these nanoparticles within the biological system. Understanding PK (Pharmacokinetics) and PD (Pharmacodynamics) of nanoparticles is vital for optimizing drug delivery, ensuring efficacy, and minimizing potential side effects when using these nanoscale carriers for targeted therapies. Additionally, PK/PD studies guide the design of nanoparticle-based drug delivery systems, contributing to safer and more efficient healthcare solutions [11]. Before delving into PK/PD of nanoparticles, it is essential to have a comprehensive understanding of the current global scenario of NDDS.

The global NDDS market was estimated to be valued at approximately US$12.7 billion in year 2022. Projections indicate that it is poised to reach a revised market size of around US$61 billion by the year 2030, demonstrating a compounded annual growth rate (CAGR) of 21.6% over the analysis period spanning from 2022 to 2030. The NDDS market in the United States is estimated to be valued at approximately US$4.8 billion in 2022. China, as the world's second-largest economy, is expected to reach a projected market size of around US$7.4 billion by 2030, exhibiting a CAGR of 26.4% during the analysis period from 2022 to 2030. Noteworthy growth is also anticipated in other geographic markets, including Japan and Canada, which are forecast to experience growth rates of approximately 18.7% and 19.8%, respectively, over the period spanning from 2022 to 2030. In Europe, Germany is expected to grow at a CAGR of approximately 20.2% [12].

"Nanotechnology—Over a Decade of Progress and Innovation": A report by the USFDA, issued in July 2020 illustrates the increasing trend in Investigational New Drug (IND), New Drug Application (NDA), Abbreviated New Drug Application (ANDA) submissions of human drug products to the USFDA that involve nanomaterials from 1970 to 2019 [13], as shown in Fig. 1.1.

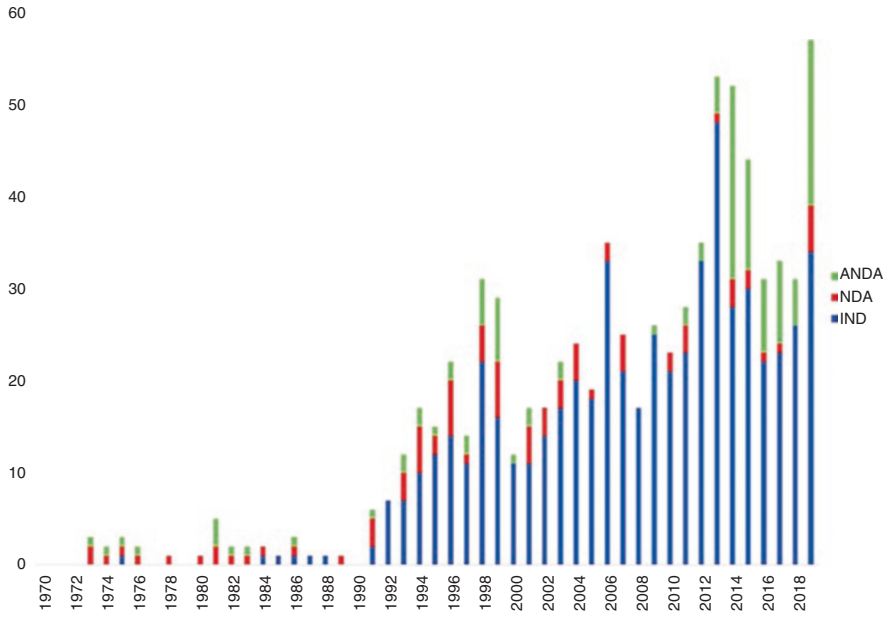

Fig. 1.1 Nanomaterials based applications submitted to the United States Food and Drug Administration (USFDA) in the period of 1970–2019 (Figure adapted from USFDA website data freely available in public domain: "Nanotechnology—Over a Decade of Progress and Innovation: A report by the USFDA") [13]

The growth of the NDDS market is driven by a combination of medical, technological, regulatory, and economic factors, with a focus on improving patient outcomes and treatment options [14], including:

Chronic Diseases: The rising prevalence of chronic diseases, such as cancer, diabetes, and cardiovascular diseases, creates a demand for advanced drug delivery systems to improve treatment outcomes.

Biopharmaceuticals: The growth of biopharmaceuticals, including monoclonal antibodies and gene therapies, has spurred the development of specialized drug delivery technologies to enhance their delivery and effectiveness.

Personalized Medicine: The shift towards patient-centric healthcare and personalized medicine is fueling the demand for tailored drug delivery systems that meet individual patient needs.

Population: The aging population in many countries is driving the need for innovative drug delivery systems to address age-related health conditions.

Technological Advancements: Advances in nanotechnology, materials science, and microfabrication have opened up new possibilities for creating novel drug delivery platforms.

Regulatory Support: Favourable regulatory policies and incentives for innovative drug delivery systems encourage companies to invest in research and development.

Investment and Research: Significant investments in research and development by pharmaceutical companies, startups, and government initiatives are fueling innovation in drug delivery technologies.

Global Pandemic: The COVID-19 pandemic has accelerated research into vaccine delivery systems, including nanoparticle-based platforms, which will likely have lasting impacts on pharmaceutical industry [15].

As nanotechnology continues to evolve, the range and impact of marketed nanotechnological products are expected to grow, shaping the future of industries and improving the quality of life for people around the world. Over the past few decades, nanotechnology has transitioned from laboratory research to translational applications, leading to the emergence of a wide range of nanotechnological products in the global market. Table 1.1 summarises various approved nanotechnology based marketed formulations.

The translation of NDDS from the laboratory to commercialization is a complex and multifaceted process. While these technologies hold the potential to revolutionise healthcare, there are several challenges that companies and researchers must address to successfully commercialise these innovations. Several factors contribute to these translational gaps are as follows [19]:

(a) **Complexity of nanostructures:** Nano formulations involve complex structures with precise control over size, shape, surface properties, and drug loading. Scaling up these complex structures while maintaining their integrity and functionality is highly challenging.
(b) **Regulatory hurdles:** Regulatory agencies like the USFDA and EMA (European Medicines Agency) have stringent requirements for approving new drug formulations, especially those involving nanoparticles. Demonstrating safety and efficacy, characterizing the product's quality, and ensuring consistent manufacturing processes is time-consuming and expensive.
(c) **Biocompatibility and toxicity:** Nanoformulations must be carefully evaluated for their biocompatibility and potential toxicity. This requires extensive preclinical studies to understand their effects in different biological systems.
(d) **Stability and shelf life:** Maintaining the stability of nano formulations over time is crucial for commercial viability. Ensuring that nanoparticles remain stable, both in storage and during administration, is challenging.
(e) **Scalability:** Transitioning from small-scale laboratory production to large-scale commercial manufacturing is tough. Achieving the same level of precision and quality control at scale is a significant hurdle.
(f) **Cost-effectiveness:** The production of nanoparticles often involves expensive and specialized equipment and materials. Reducing the cost of manufacturing while maintaining quality is significant barrier to translation.
(g) **Targeted delivery and efficacy:** While nano formulations offer the promise of targeted drug delivery, ensuring that the nanoparticles effectively reach their intended target and produce the desired therapeutic effect is complex and requires further optimization.

Table 1.1 List of approved marketed nano formulations [16–18]

Sr. no	Formulation type	Name of the product	Name of drug	Manufacturer	Use
1	Liposomal formulation	Doxil® (Caelyx™)	Doxorubicin	Janssen Pharmaceuticals	Multiple myeloma, ovarian neoplasms, breast neoplasms, Kaposi sarcoma
		Onivyde®	Irinotecan	PharmaEngine	Metastatic pancreatic cancer
		Vyxeos®	Daunorubicin and Cytarabine	Jazz Pharmaceuticals	Treatment of certain types of acute myeloid leukemia
		DepoDur®	Morphine	Pacira Pharmaceuticals Ltd.	Post-operative pain management
		AmBisome®	Amphotericin B	Gilead Sciences International Ltd.	Severe systemic and deep mycoses and visceral leishmaniasis in immunocompetent patients
		DaunoXome®	Daunorubicin	Galen Limited	Treatment of advanced HIV-associated Kaposi's sarcoma
		Myocet®	Doxorubicin	Cephalon Europe	Breast neoplasms
		DepoCyte®	Cytarabine	Pacira Pharmaceuticals Ltd.	Meningeal neoplasms
		Marqibo®	Vincristine	Talon Therapeutics	Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia
		Visudyne®	Verteporfin	Bausch & Lomb Incorporated	Degenerative myopia, age related macular degeneration
		Mepact®	Mifamurtide	IDM Pharma SAS	Osteosarcoma
		Epaxal®	Hepatitis A vaccine	Crucell Italy	Active immunisation against hepatitis A

(continued)

Table 1.1 (continued)

Sr. no	Formulation type	Name of the product	Name of drug	Manufacturer	Use
2	Polymeric nanoparticles	Abraxane®	Paclitaxel (Albumin-bound nanoparticles)	Celgene Corporation (now part of Bristol Myers Squibb)	Metastatic breast cancer
		Gebexol-PM®	Paclitaxel (Methoxy-PEG-poly[D,L-lactide] taxol)	Lupin Ltd	Breast cancer, pancreatic cancer, and non-small cell lung cancer
		Oncaspar®	(PEG-L-asparaginase)	Servier IP UK Ltd	Acute lymphoblastic leukaemia
		Neulasta®	PEG-filgrastim	Amgen Inc	Used to prevent neutropenia
		Rapamune®	Sirolimus (also known as Rapamycin) (Colloidal dispersion of nanocrystals stabilized with poloxamer)	Pfizer	Prophylaxis of organ rejection in renal transplant
		Emend®	Aprepitant (Colloidal dispersion of nanocrystals)	Merck Sharp & Dohme Corp	Nausea and vomiting
		Cholib®	Fenofibrate/Simvastatin (Colloidal dispersion of nanocrystals)	Abott Healthcare Products Ltd	Dyslipidemias
3	Metallic nanoparticles	Feraheme®	Ferumoxytol (superparamagnetic iron oxide nanoparticles)	AMAG Pharmaceuticals	Iron replacement therapy for iron-deficiency anemia
		NanoTherm®	Iron oxide nanoparticle	MagForce AG	Multiple myeloma
		Hensify® (NBTXR3)	Hafnium oxide nanoparticles stimulated with external radiation to enhance tumor cell death via electron production	Nanobiotix	Locally advanced squamous cell carcinoma
4	Lipidic nano formulations	Intralipid®	Lipid-based nanoemulsion of essential fatty acids and vitamins	Fresenius Kabi	Emergency management of local anaesthetics inadvertently administered intravenously
		Onpattro® (Patisiran) ALN-TTR02	Lipid nanoparticle RNAi for the knockdown of disease-causing TTR protein	Alnylam Pharmaceuticals	Transthyretin (TTR)-mediated amyloidosis

(h) **Clinical trials:** Conducting clinical trials to demonstrate the safety and efficacy of nano formulations is time-consuming and expensive. Moreover, recruiting patients for such trials is tough, particularly if the formulation targets a rare disease or a niche market.
(i) **Market adoption:** Even if a nanoformulation successfully traverses the regulatory process and demonstrates clinical efficacy, market adoption may be slow owing to factors such as physician acceptance and competition with established therapeutic modalities.
(j) **Intellectual property:** Protecting intellectual property associated with nanoformulations can be challenging and hinders their translation.

To bridge the translational gap for nanoformulations, collaboration among researchers, clinicians, regulatory agencies, and industry stakeholders is essential. Additionally, continued investment in research, development, and the establishment of standardized protocols for evaluation and manufacturing can help overcome some of these challenges.

1.2 Regulatory Guidelines for NDDS in Pharmaceutical Industry

Food products, cosmetics, medical devices, and medications have incorporated nanotechnology over the course of several decades. There is a wide range of pharmaceuticals incorporating nanomaterials that are under the jurisdiction of the USFDA's Centre for Drug Evaluation and Research (CDER). The number of authorised drug products utilising nanomaterials has steadily increased, which includes generic medications as well as experimental novel pharmaceuticals, new drug applications, and abbreviated new drug applications. Since the early 1970s, more than 60 applications have been accepted, and the demand continues to grow [20]. Current nanotechnology research is concentrated on the exploration of pivotal processes and material attributes that possess the potential to influence product quality, while comprehending quality within the broader framework of effectiveness and safety. The stability of liposomes, is also a significant aspect under scrutiny, given its direct bearing on product quality. Additionally, there is a focus on assessing the extent to which manufacturing deviations, such as temperature fluctuations or drying procedures, can affect particle size, distribution within the body, and overall stability.

Manufacturers are obligated to meticulously opt for and execute suitable quality control measures to enable the detection of any potential variations in the nanoproduct. The Office of Testing and Research (OTR) focuses their attention on assessing the drug's performance through the utilization of advanced analytical techniques. These assessments include examinations conducted both within the body (*in-vivo*) and in external settings (*in-vitro*). The primary objectives are to unravel the mechanisms governing the release of the drug from nanocarriers and to establish a correlation between *in-vivo* and *in-vitro* findings [21].

In 2014, the formation of the Nanotechnology Risk Assessment Working Group aimed to evaluate the implications of nanotechnology on drug products. Comprising of experts from various domains within the CDER, this working group is actively engaged in establishing standards for nanomaterials applied in drug development, thereby fostering technological progress. The collective findings of this working group indicate that, for the most part, current assessment procedures suffice for the evaluation of drugs incorporating nanomaterials. However, this is contingent upon the drug applicant's diligent execution of appropriate studies early in the developmental phase and the implementation of a formulation control strategy to ensure consistent clinical outcomes. The CDER has dedicated substantial efforts over recent years to comprehend the attributes of nanomaterials when utilized in drug products. This aims to establish a regulatory framework that can effectively evaluate the influence of these unique physical properties on the safety and efficacy of such nanotechnology-based products. The initial phase of this work concentrated on exploring the role of zinc oxide and titanium dioxide nanomaterials in sunscreens. CDER conducted studies to investigate the potential penetration of titanium dioxide nanomaterials into normal skin, demonstrating in pig model that such penetration did not occur beyond the dermis. In more recent times, CDER's ongoing research initiatives encompass a broader scope, including the characterization and safety assessment of nanomaterials in drug products [22].

The USFDA has released a series of guidance documents concerning the utilization of nanotechnology in products that fall under FDA regulation. These guidance documents are being issued as a part of the USFDA's ongoing efforts to implement the recommendations outlined in the FDA's 2007 Nanotechnology Task Force Report. It is important to note that while these guidance documents do not establish or grant any rights to individuals or impose binding obligations on the FDA or the public, they do serve as a reflection of the FDA's current perspective on the subject matter. Some of the guidance documents that address the use of nanotechnology or nanomaterials in products regulated by the FDA are discussed in Table 1.2:

The existing regulatory framework in Europe actively supports the advancement of novel nanomedicines and has demonstrated its efficacy in evaluating marketing authorization applications for such products. A substantial commitment is being made both at the European and international levels to ensure that regulatory science progresses in sync with the evolving knowledge of nanotechnology. In 2007, the EMA, in collaboration with experts from regulatory agencies in the United States, Japan, Canada, and Australia, participated in a global initiative led by the FDA. This initiative aimed to establish the defining characteristics of medicines utilizing nanotechnology. The consortium of regulatory bodies engaged in discussion and information sharing on guidelines as well as scientific and legislative efforts in their respective regions. This exchange of information and experience facilitated valuable insights, drawing from analogous frameworks such as cosmetics, medical devices, and consumer products. Under the chairmanship of the EMA, this group also formulated a working descriptor for "nano-medicines intended for internal use." This descriptor served as a common reference point to enable global regulatory authorities to exchange experiences and deliberate on their respective

Table 1.2 Summary of USFDA's Final Guidance to Industry on use of nanotechnology

Sr. no	Final Guidance for Industry	Summary	Ref
1	Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives.	This document offers guidance to food ingredient and food contact substance (FCS) manufacturers, as well as end users of food ingredients categorized as color additives. The guidance outlines the FDA's current perspective on evaluating the impact of substantial changes in manufacturing processes, such as the incorporation of nanotechnology, on the safety and regulatory status of a food substance.	[23]
2	Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology	This guidance document establishes a comprehensive framework for the FDA's regulatory approach to nanotechnology products. It is intended to serve as a reference for manufacturers, suppliers, importers, and various stakeholders. Within this framework, it highlights two critical factors that should be taken into account when determining whether a product, subject to FDA regulation, incorporates nanotechnology: a) Whether a material or end product has been intentionally engineered to possess at least one external dimension, internal structure, or surface feature falling within the nanoscale range, which spans approximately 1 nanometer (nm) to 100 nanometers (nm). b) Whether a material or end product has been purposely designed to exhibit specific properties or phenomena, encompassing physical, chemical, or biological effects, which can be attributed to its dimensions. This evaluation applies even if these dimensions extend beyond the nanoscale range, up to 1 μm (1000 nm).	[24]

(continued)

Table 1.2 (continued)

Sr. no	Final Guidance for Industry	Summary	Ref
3	Final Guidance for Industry: Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation.	This guidance document outlines the specific information that should be included in a new drug application (NDA) or abbreviated new drug application (ANDA) for a liposome drug product, which is subject to review by the Center for Drug Evaluation and Research (CDER). The discussion within this guidance encompasses the following key areas related to liposome drug products: a) Chemistry, Manufacturing, and Controls (CMC): This section provides guidance on the submission of information pertaining to the chemistry, manufacturing, and quality control of liposome drug products. b) Human Pharmacokinetics and Bioavailability (or Bioequivalence, in the case of an ANDA): This part offers recommendations regarding the submission of data on human pharmacokinetics and bioavailability, which are crucial aspects of evaluating the effectiveness and safety of liposome drug products. c) Labeling in NDAs and ANDAs: This section addresses the labeling requirements and recommendations for liposome drug products included in NDAs and ANDAs. The guidance primarily focuses on the distinct technical considerations associated with liposome drug products.	[25]
4	Final Guidance for Industry: Safety of Nanomaterials in Cosmetic Products	This guidance document offers industry professionals and various stakeholders, including academia and other regulatory bodies, insights into the FDA's current perspective on the safety evaluation of nanomaterials present in cosmetic products. Its primary aim is to aid industry players and stakeholders in the identification of potential safety concerns associated with nanomaterials in cosmetic formulations and in the establishment of a structured approach for their evaluation. Furthermore, this guidance document includes contact information for manufacturers and sponsors interested in engaging with the FDA to discuss safety-related matters concerning the utilization of specific nanomaterials in cosmetic products. This serves as a channel for dialogue and consultation on safety considerations in these cases.	[26]

5	Final Guidance for Industry: Use of Nanomaterials in Food for Animals	This guidance document outlines the current stance of the Food and Drug Administration (FDA) regarding the use of nanomaterials and the application of nanotechnology in animal food. Its purpose is to assist industry professionals and other stakeholders in recognizing potential concerns related to the safety and regulatory status of animal food that either contains nanomaterials or involves the utilization of nanotechnology. In this context, "animal food" refers to food intended for consumption by animals.	[27]
6	Final Guidance for Industry: Drug Products, Including Biological Products, that Contain Nanomaterials	This guidance document offers direction regarding the development of human drug products, including biological products, that incorporate nanomaterials within the final dosage form. It centers on pertinent considerations concerning the FDA's regulation of such drug products in accordance with the Federal Food, Drug, & Cosmetic Act (FD&C Act) and Public Health Service Act (PHS Act). The guidance is intended to provide recommendations to applicants and sponsors of investigational, premarket, and postmarket submissions for these specific products.	[28]

approaches to regulating this emerging field. It ensured that regulatory science advancements were collaborative and open to input from various stakeholders, including the work of ISO 199 TC. Building upon the collaborative work of this international expert group, the EMA organized the First International Scientific Workshop on Nanomedicines on September 2–3, 2010. The workshop brought together approximately 200 participants from Europe and around the world, representing 27 countries, including Australia, Canada, India, Japan, and the United States. These participants engaged in discussions concerning the advantages and challenges associated with the application of nanotechnologies in medicine [24, 29].

1.3 Need of Pharmacokinetic and Pharmacodynamic Studies (PK/PD) of NDDS

Understanding pharmacokinetics and pharmacodynamics play a significant role in overcoming the translational challenges of NDDS. PK/PD studies are essential in evaluating the impact of these nano systems, which aim to enhance drug efficacy and safety through controlled and targeted release as shown in Fig. 1.2.

PK is the study of how the body interacts with a drug after administration. It involves the processes of absorption, distribution, metabolism, and excretion (ADME) that a drug undergoes within the body. In the context of novel drug delivery systems, understanding pharmacokinetics becomes crucial for optimizing drug release profiles, extending drug circulation times, and achieving targeted delivery. Various routes of administration, including oral, parenteral, transdermal, and inhalation, offer distinct pharmacokinetic profiles that influence the design and selection of delivery systems. By studying the PK of novel drug delivery systems, researchers can assess their bioavailability, tissue distribution, and elimination kinetics. This knowledge helps optimize dosage regimens, predict drug concentrations at the target site, and determine the duration of therapeutic effect. On the other hand, PD refers to the study of a drug's mechanism of action and its effects on the body. It encompasses receptor binding, signal transduction, and the resulting physiological responses. Novel drug delivery systems often aim to enhance pharmacodynamic outcomes by providing controlled and sustained drug release, localized drug action, or modulation of drug release in response to specific physiological cues. PD studies of NDDS provide insight into their mechanism of action, therapeutic efficacy, and potential side effects [11].

PK/PD studies of NDDS provide valuable insights into the behavior of drugs and nanoparticles in the body, their interactions with biological systems, and their therapeutic effects. Understanding PK/PD of nanoformulations helps in [30]:

(a) **Optimizing drug delivery:** PK studies help determine the ADME of nanoformulations. This information guides the designing of nanoparticles to enhance drug delivery. For example, understanding the drug's PK profile can help modify the nanoparticles to improve drug release kinetics, bioavailability, and tissue-specific targeting.

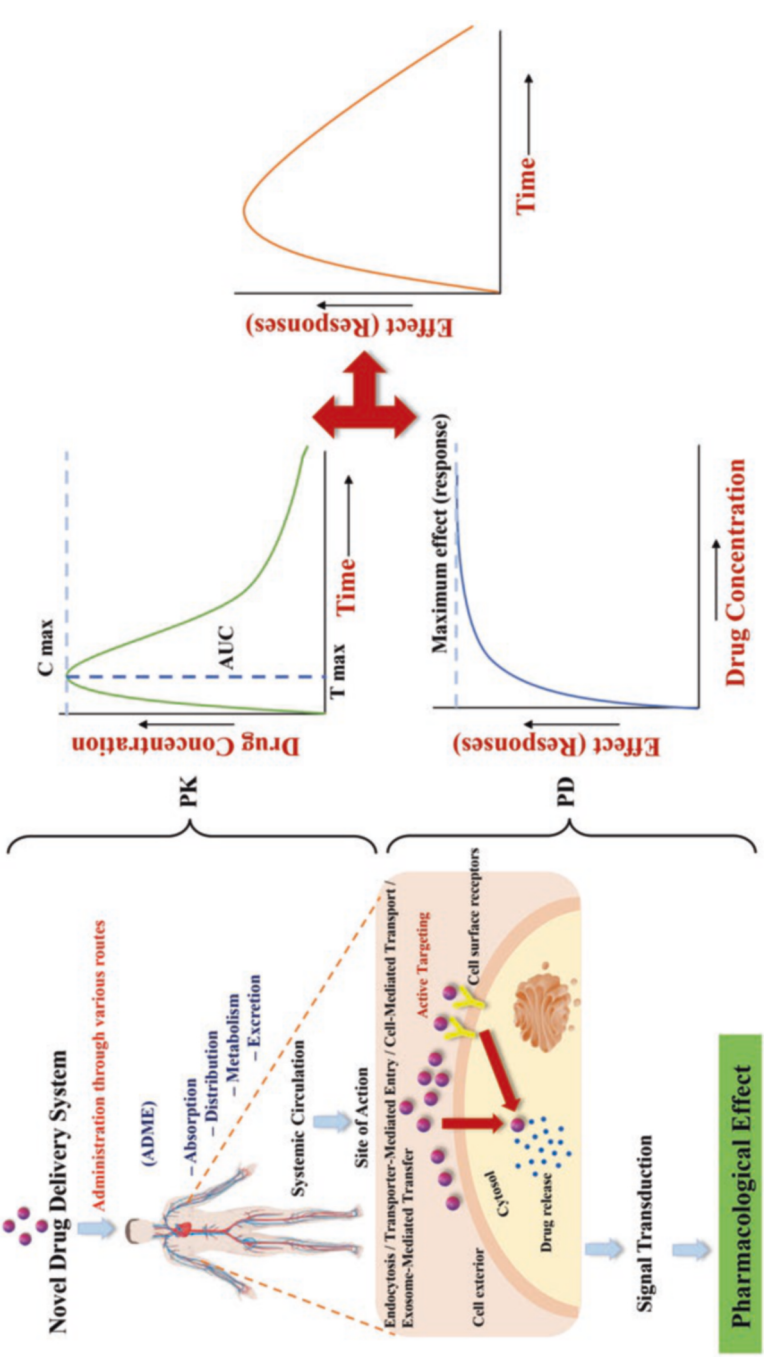

Fig. 1.2 Pharmacokinetics (PK) and pharmacokinetics (PD) of nanoparticles; (*AUC* area under the curve, *Cmax* maximum drug concentration, *Tmax* time taken by the drug to reach maximum concentration)

(b) **Dosing regimen:** PD studies elucidates the relationship between drug concentration and therapeutic effect. This knowledge helps to establish the appropriate dosing regimen of nanoformulations, ensuring that the drug concentration remains within the therapeutic window while minimizing side effects.
(c) **Minimizing toxicity:** PK studies identify potential toxicity associated with nanoformulations, such as accumulation of nanoparticles in specific tissues. Understanding the distribution of nanoparticles in the body and their clearance rates helps design safer formulations.
(d) **Predicting clinical efficacy:** PD studies help establish a dose-response relationship, enabling researchers to predict the clinical efficacy of nanoformulations. This information is crucial for designing effective clinical trials and determining appropriate endpoints.
(e) **Patient stratification:** PK/PD data helps identify patient populations that are most likely to benefit from nanoformulations. This personalized medicine approach improves the chances of success in clinical trials and enhances the value proposition of the nanoformulation.
(f) **Biomarker development:** PK/PD studies aids in the identification of biomarkers that correlate with therapeutic response or toxicity. These biomarkers serve as valuable tools for patient selection, monitoring treatment efficacy, and predicting treatment outcomes.
(g) **Regulatory approval:** Regulatory agencies require comprehensive PK/PD data as part of the drug approval process. A thorough understanding of the behavior of the drug in the body can facilitate and streamline the approval process for nanoformulations.
(h) **Dose optimization:** PK/PD modeling and simulations helps optimize dosing regimens, reducing the risk of underdosing or overdosing patients. This is particularly important for nanoformulations, where drug release and distribution is complex.
(i) **Long-term safety:** PK studies provide insights into the long-term safety of nanoformulations by monitoring drug and nanoparticle persistence in the body. This information helps in addressing concerns about potential accumulative toxicity.
(j) **Translational success:** A robust understanding of PK/PD can improve the predictability of a nanoformulations performance in humans, reducing the likelihood of translational failures. This can save time and resources in the drug development process.

In summary, PK/PD studies are essential tools for characterizing the behavior of nanoformulations *in-vivo* and optimizing their design for clinical use. They provide crucial data for regulatory submissions, dose selection, patient stratification, and overall translational success. Incorporating PK/PD insights into the development process can enhance the probability of successful translation and commercialization of nanoformulations. While PK/PD studies offer numerous advantages in the development of NDDS, they also introduce unique challenges. Some challenges specific to the PK/PD aspects of NDDS are as follows [31–34]:

(a) **Complex pharmacokinetics:** The complex nature of NDDS leads to more complex PK profiles. Factors such as drug release rates, particle size, surface characteristics, and carrier interactions influence drug absorption, distribution, and elimination.
(b) **Variability in drug release:** NDDS often exhibit controlled or sustained drug release profiles, leading to variability in drug exposure. This variability requires careful consideration and adjustments to ensure consistent therapeutic effects.
(c) **Non-linear pharmacokinetics:** Some NDDS exhibit non-linear PK, where changes in dose do not lead to proportional changes in drug concentration. Understanding and predicting these non-linear relationships can be challenging.
(d) **Tissue distribution and accumulation:** Targeted NDDS alters the tissue distribution pattern of drugs. Achieving desired drug accumulation at target sites while minimizing off-target accumulation can be complex and depends on factors like particle size, surface modification, and targeting ligands.
(e) **Stability and degradation:** NDDS have significant impact on the drug stability and its susceptibility towards degradation. Factors like pH, temperature, and interaction with carrier materials can impact drug stability and subsequently affect PK.
(f) **Interactions with biological carriers:** NDDS often interact with biological barriers, such as cell membranes and the blood-brain barrier and these interactions influence the ADME of encapsulated drugs. Biological responses to NDDS are further more complex and multifaceted, influenced by factors beyond drug release, such as carrier-cell interactions and immune responses.
(g) **Biocompatibility and immunogenicity:** Some NDDS triggers immune responses or adverse reactions, affecting both PK and PD. Evaluating the biocompatibility and potential immunogenicity of these materials is important.
(h) **Dosing strategies:** Determining appropriate dosing strategies for NDDS is challenging. Balancing the release profile with therapeutic efficacy and safety considerations requires careful optimization.
(i) **PK/PD modeling:** Developing accurate PK/PD models for NDDS is complex due to the numerous variables involved. Specialized modeling approaches are often needed to accurately predict the drug behavior.
(j) **Targeting and non-targeting effects**: NDDS offer targeted delivery, however unintended interactions with off-target tissues can occur, affecting both PK and PD responses.
(k) **Patient variability:** The impact of NDDS on PK/PD can vary among individuals due to genetic, physiological, and disease-related factors. Individualized treatment approaches may be needed.
(l) **In-vivo validation:** NDDS require in-vivo validation to assess PK/PD behavior accurately. Designing and conducting these studies can be resource-intensive.
(m) **Long-term effects:** Understanding the long-term PK/PD effects of NDDS, especially in chronic diseases, requires extensive research to ensure safety and sustained therapeutic benefits.

Addressing these challenges requires interdisciplinary collaboration among formulation scientists, pharmacologists, material scientists, clinicians, and regulatory experts. Combining in vitro studies, preclinical assessment, advanced modeling techniques, and clinical trials is essential to comprehensively understand and optimize the PK/PD behavior of NDDS, ensuring their safe and effective translation from the lab to clinical practice.

1.4 Conclusion

The advent of novel drug delivery systems has revolutionized the pharmaceutical industry by offering improved therapeutic outcomes and patient comfort. As NDDS continues to evolve, they hold promise of transforming the future of medicine, making treatments more effective, accessible to individual health conditions. The study of PK/PD of nanoparticles represents a dynamic and rapidly evolving field with immense potential for improving drug delivery and patient outcomes. The subsequent chapters delve deeper into PK/PD of specific delivery systems, and their applications.

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Chapter 2
Absorption, Distribution, Metabolism and Excretion of Novel Drug Delivery Systems

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Introduction by the Editor

Nanotechnology has revolutionized various fields, from drug delivery to diagnosis, by enabling the designing and engineering of drug carriers at the nanoscale level. Nanoparticles, possess unique properties that make them highly valuable in numerous applications. However, understanding how these nanoparticles are absorbed, distributed, metabolized, and excreted within biological systems is crucial for ensuring their safe utilization [1]. Once inside the body, nanoparticles get distributed across different tissues and organs, facilitated by their unique physicochemical characteristics as depicted in Fig. 2.1. It is therefore important to understand the factors that affect the absorption, distribution, metabolism and excretion (ADME) of nanoparticles. The factors affecting ADME of nanoparticles are as follows [2–4]:

(a) Physicochemical properties of nanoparticles (size, shape, surface area to volume ratio, surface charge, surface coating, surface chemistry, surface topology, crystallinity, functionalization, PEGylation, ligand conjugation, composition of nanoparticles, density, porosity, solubility of nanoparticles, stability and aggregation potential of nanoparticles)
(b) Route of administration of nanoparticles and type of delivery system

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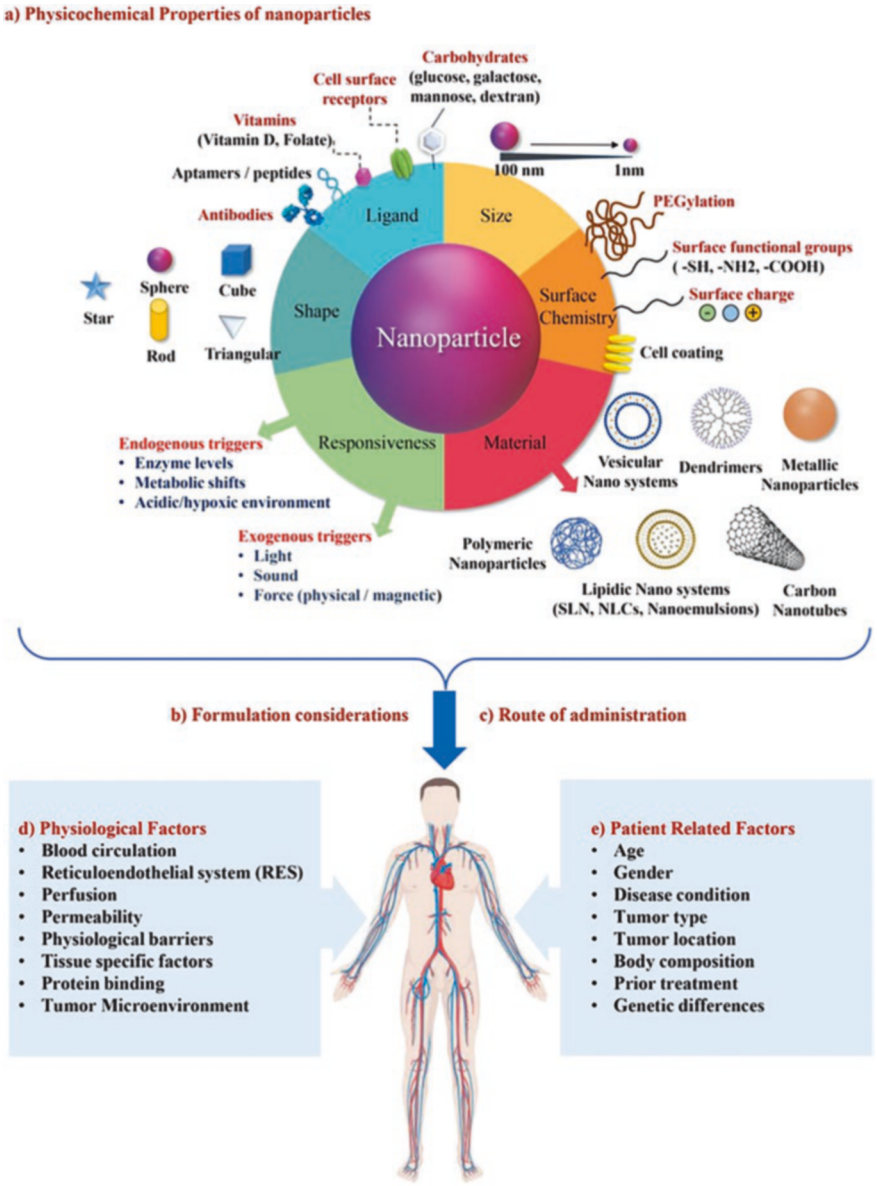

Fig. 2.1 Factors affecting absorption, distribution, metabolism, excretion of nanoparticles

(c) Physiological factors (Blood circulation, Reticuloendothelial system (RES) interaction, perfusion, permeability, physiological barriers, tissue specific factors, protein binding)
(d) Patient related factors (age, gender, disease type, tumor type and location, body composition and prior treatments)