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MICROPLASTICS AND NANOPLASTICS AS EMERGING MODIFIERS OF HUMAN DRUG PHARMACOKINETICS: IMPLICATIONS FOR ADME AND THERAPEUTIC OUTCOMES

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ABSTRACT

Introduction: Microplastics (MPs) and nanoplastics (NPs) are ubiquitous environmental contaminants that may influence human drug pharmacokinetics. Their small size, large surface area, and diverse surface chemistries enable adsorption of drugs, modulation of intestinal barriers, and interactions with metabolic enzymes and transporters, potentially altering absorption, distribution, metabolism, and excretion (ADME). **Methods:** A comprehensive literature search was performed in PubMed, Scopus, Web of Science, and Google Scholar using keywords including “microplastics,” “nanoplastics,” “ADME,” “pharmacokinetics,” and “drug–particle interactions.” In vitro, in vivo, and human biomonitoring studies, along with relevant physiologically based pharmacokinetic (PBPK) modeling, were reviewed to evaluate mechanistic evidence and clinical implications. **Results:** Experimental data indicate that MPs/NPs can adsorb drug molecules, disrupt tight junctions, modulate transporter activity (e.g., P-gp, OATP), and alter hepatic enzyme expression (CYP450 isoforms). Nanoplastics can translocate across epithelial barriers, interact with plasma proteins, and accumulate in tissues, affecting systemic drug exposure. Drugs with narrow therapeutic windows—including antiepileptics, anticoagulants, and biologics—are particularly vulnerable. Co-exposure with environmental pollutants such as heavy metals or endocrine disruptors may exacerbate these effects. While mechanistic insights from cellular and animal studies are substantial, human pharmacokinetic evidence remains limited. **Conclusion:** MPs and NPs

represent emerging modulators of drug disposition, with potential consequences for efficacy and safety. Integrating biomonitoring, PBPK modeling, and multi-omics approaches is essential to assess real-world impacts. Recognition of particle-mediated drug interactions is critical for precision pharmacotherapy, regulatory evaluation, and development of mitigation strategies for populations chronically exposed to environmental plastics.

KEYWORDS: Microplastics; Nanoplastics; Drug–particle interactions; Pharmacokinetics; ADME; Therapeutic efficacy.

INTRODUCTION

The widespread and persistent contamination of the environment by microplastics and nanoplastics has emerged as a defining toxicological concern of the twenty-first century. Microplastics are generally defined as plastic particles smaller than 5 mm, while nanoplastics are typically considered to be below 1 µm in diameter.[1] These particles originate from the degradation of larger plastic debris as well as from primary sources such as industrial abrasives, cosmetic additives, and synthetic fibers.[2] They have been detected in marine and freshwater systems, agricultural soil, food products, drinking water, and indoor air.[3] Human exposure is therefore continuous and occurs primarily through ingestion and inhalation, with dermal contact representing an additional but less characterized route.[4]

Recent biomonitoring studies have confirmed the presence of microplastic particles in human stool, blood, lung tissue, placenta, and even breast milk, raising concerns regarding systemic distribution and biological interaction.[5,6] Unlike conventional environmental toxicants that exert effects through defined chemical pathways, microplastics and nanoplastics possess both particulate and chemical properties.[7] Their biological activity is shaped not only by polymer composition such as polyethylene, polypropylene, polystyrene, and polyvinyl chloride, but also by particle size, surface charge, hydrophobicity, aging status, and the adsorption of environmental contaminants.[8] These physicochemical characteristics collectively determine their capacity to cross epithelial barriers, interact with cellular membranes, and participate in molecular binding events.[9]

Parallel to the expanding literature on plastic-associated toxicity, pharmacokinetics remains central to the rational use of medicines.[10] The processes of absorption, distribution, metabolism, and excretion determine systemic drug exposure, therapeutic efficacy, and toxicity risk.[11] Subtle modifications in gastrointestinal permeability, plasma protein binding,

hepatic enzyme activity, or renal clearance can substantially alter pharmacokinetic parameters such as bioavailability, maximum plasma concentration, area under the curve, and elimination half-life.[12] Environmental modifiers of drug disposition are increasingly recognized; for example, dietary components, gut microbiota composition, and co-exposure to pollutants can influence cytochrome P450 activity and drug transporter expression.[13] Within this broader context, microplastics and nanoplastics represent a plausible but underexplored class of pharmacokinetic modifiers.

Several mechanistic pathways support the hypothesis that these particles may alter human drug disposition.[14] First, the large surface-area-to-volume ratio of small plastic particles facilitates adsorption of hydrophobic and amphiphilic drug molecules.[15] Such adsorption may occur within the gastrointestinal lumen, potentially reducing free drug availability for absorption or, conversely, acting as a secondary reservoir that prolongs exposure.[16] Second, nanoplastics are capable of translocating across intestinal epithelium via paracellular diffusion, endocytosis, or M-cell–mediated transport.[17] Once in systemic circulation, they may interact with plasma proteins, forming a dynamic protein corona that competes with drug binding sites and alters distribution patterns.[18]

Third, accumulating experimental evidence indicates that microplastics and nanoplastics can induce oxidative stress, inflammatory signaling, and mitochondrial dysfunction in hepatic and intestinal cells.[19] These processes are closely linked to modulation of drug-metabolizing enzymes, particularly cytochrome P450 isoforms, as well as phase II conjugation systems.[20,21] Altered enzyme expression or activity may lead to unpredictable changes in drug clearance, especially for medications with narrow therapeutic indices.[22] Furthermore, disruption of membrane integrity and tight junction proteins in epithelial barriers suggests potential effects on transporter proteins such as P-glycoprotein, breast cancer resistance protein, and organic anion transporting polypeptides, all of which are critical determinants of drug absorption and distribution.[23]

Renal function may also be influenced. Experimental models have shown that plastic particles can accumulate in kidney tissue and provoke tubular injury or inflammatory responses.[24] Such alterations could theoretically impair glomerular filtration or active secretion processes, thereby modifying drug elimination kinetics. In addition, interactions between microplastics and the gut microbiome introduce another layer of complexity, as

microbial metabolism contributes to the biotransformation of certain drugs and regulates host enzyme expression.[25]

Despite these biologically plausible mechanisms, the intersection between microplastic exposure and pharmacokinetics has not been systematically synthesized. Most available studies focus on toxicological endpoints rather than on changes in drug concentration–time profiles or therapeutic outcomes. As global plastic production continues to rise and environmental contamination intensifies, understanding how chronic low-level exposure may influence medication response becomes increasingly relevant. This is particularly important for vulnerable populations, including pregnant women, older adults, and patients receiving long-term pharmacotherapy for chronic diseases.

This review aims to critically examine current evidence supporting microplastics and nanoplastics as emerging modifiers of human drug pharmacokinetics. By integrating data from in vitro experiments, animal studies, biomonitoring research, and pharmacological theory, we seek to elucidate potential mechanisms affecting absorption, distribution, metabolism, and excretion. In doing so, we highlight implications for therapeutic efficacy, toxicity risk, and future regulatory considerations. Recognizing microplastics not only as environmental contaminants but also as potential determinants of drug disposition may open a new interdisciplinary field at the interface of environmental health and clinical pharmacology.

METHODOLOGY

This review was based on a comprehensive literature search and critical analysis of studies on microplastics (MPs), nanoplastics (NPs), and their potential impact on human drug pharmacokinetics. Databases including PubMed, Scopus, Web of Science, and Google Scholar were searched using keywords such as “microplastics”, “nanoplastics”, “ADME”, “pharmacokinetics”, and “drug–particle interaction”. Both in vitro and in vivo studies, human biomonitoring reports, and relevant pharmacological modeling studies were included, while articles focusing solely on plastic toxicity were excluded. Data on particle characteristics, exposure routes, experimental models, and effects on absorption, distribution, metabolism, and excretion were extracted and synthesized. Physiologically based pharmacokinetic (PBPK) modeling studies were included when available to illustrate quantitative interactions. The review integrates findings across environmental science, pharmacology, and clinical

relevance to provide a clear understanding of how MPs and NPs may influence drug behavior in humans.

1. Physicochemical Characteristics Relevant to Drug Interaction

The interaction between microplastics and nanoplastics and pharmaceutical compounds is largely governed by their physicochemical properties. Unlike dissolved chemicals, these particles act as dynamic colloidal systems whose size, surface chemistry, and environmental history determine their behavior in biological fluids. Understanding these properties is essential for predicting how they may influence drug adsorption, epithelial transport, systemic distribution, and cellular responses. **Table 1** summarizes key particle characteristics of microplastics (MPs) and nanoplastics (NPs) that affect their interactions with drugs.

1.1 Size, Surface Area, and Charge

Particle size is a key determinant of how plastics interact biologically.[26] As particle diameter decreases, the surface-area-to-volume ratio rises sharply, giving nanoplastics extensive surfaces for adsorbing drug molecules, particularly hydrophobic and amphiphilic compounds, through hydrophobic interactions, van der Waals forces, electrostatic attraction, or π–π stacking depending on both drug structure and polymer surface characteristics.[27,28] Smaller particles can cross biological barriers more easily, undergoing transcellular transport via endocytosis or paracellular diffusion through compromised tight junctions in the gastrointestinal tract, while also interacting with mucus and epithelial cells to potentially alter drug absorption kinetics.[29] Larger microplastics, though less likely to translocate systemically, can still affect luminal drug availability by acting as sorptive matrices.[30] Surface charge further modulates these interactions; positively charged particles may adhere to negatively charged mucosal surfaces and cell membranes, enhancing retention at epithelial interfaces, whereas negatively charged particles may preferentially bind cationic drugs.[31] Charge also influences aggregation in physiological media, altering effective particle size and bioavailability, and in systemic circulation, electrostatic properties affect interactions with plasma proteins and endothelial surfaces, potentially impacting tissue distribution.[32]

1.2 Polymer Type (e.g., polyethylene, polystyrene, PVC)

The chemical composition of the polymer backbone strongly influences adsorption capacity and biological reactivity. Hydrophobic plastics like polyethylene and polypropylene favor the adsorption of lipophilic drugs via hydrophobic partitioning, while polystyrene, with its aromatic rings, can support π–π interactions with aromatic pharmaceuticals, strengthening

drug binding.[33] Polyvinyl chloride contains polar chloride groups that enable localized dipole interactions.[34] Additionally, some polymers may leach additives, plasticizers, or residual monomers, which can independently or synergistically affect enzymatic pathways or cellular stress responses, complicating pharmacokinetic predictions.[35] Structural features such as crystallinity, porosity, and surface roughness also affect sorption; more porous or irregular surfaces provide additional binding sites and can trap drug molecules within microcavities, altering desorption kinetics.[36] As a result, different polymer types vary considerably in their ability to sequester drugs in the gastrointestinal lumen or facilitate transport across epithelial barriers.

1.3 Surface Functionalization and Aging

Environmental aging processes, including ultraviolet irradiation, oxidation, mechanical abrasion, and biofouling, can substantially alter the surface chemistry of plastic particles.[37] Oxidative aging introduces polar functional groups such as hydroxyl, carbonyl, and carboxyl moieties, increasing surface hydrophilicity and modifying electrostatic properties, which may enhance the binding of polar or ionizable drugs.[38] Surface functionalization, whether naturally occurring or experimentally induced, can also change biological behavior; for example, carboxylated or aminated nanoplastics may exhibit greater cellular uptake through increased interactions with membrane proteins, while functional groups can facilitate hydrogen bonding with drugs, affecting adsorption strength and release.[39] Aging may further impact particle aggregation in physiological environments, altering effective particle size, transport across epithelial barriers, and interactions with immune cells.[40] Consequently, environmentally aged plastics can behave differently from pristine laboratory-generated particles in both drug adsorption and biological effects.[41]

1.4 Formation of Protein Corona

Upon entering biological fluids such as gastrointestinal secretions, blood, or interstitial fluid, plastic particles rapidly adsorb proteins, lipids, and other biomolecules, forming a protein corona that redefines their biological identity and influences cellular recognition, uptake, and systemic distribution.[42] This corona directly affects drug interactions: adsorbed proteins may compete with drugs for binding sites, proteins within the corona may bind drugs to form ternary complexes, and changes in surface composition can alter recognition by macrophages and endothelial cells, impacting tissue accumulation and clearance.[43] The protein corona is dynamic, evolving as particles move from the gastrointestinal tract to systemic circulation,

which can modify drug desorption kinetics and particle biodistribution.[44] This evolving interface complicates pharmacokinetic predictions and highlights the need for context-specific investigation.

Table 1: Physicochemical Properties of MPs/NPs Influencing Drug Interaction.

Property	Description	Impact on Drug Pharmacokinetics	Ref
Particle Size	Nanoplastics (<100 nm) vs microplastics (>100 nm)	Smaller particles: higher surface area, enhanced adsorption, translocation across barriers	[45]
Surface Area	Relative exposed area of particle surface	Greater adsorption capacity, potential reduction in free drug concentration	[46]
Surface Charge	Positive, negative, or neutral	Modulates interaction with drugs and membranes; affects aggregation and tissue distribution	[47]
Polymer Type	Polystyrene, polyethylene, PVC, etc.	Determines hydrophobicity, chemical reactivity, and binding affinity for drugs	[48]
Surface Functionalization / Aging	Presence of hydroxyl, carboxyl, or other groups; environmental weathering	Alters adsorption kinetics, protein corona formation, and immune recognition	[49]
Protein Corona Formation	Adsorption of plasma proteins onto particle surface	Can change particle–drug interactions, biodistribution, and cellular uptake	[50]

2. Mechanistic Basis of Interaction with ADME

Microplastics (MPs) and nanoplastics (NPs) may influence drug disposition through multiple, interconnected mechanisms affecting absorption, distribution, metabolism, and excretion (ADME).[51] These effects arise from a combination of sorptive behavior, barrier modulation, enzyme regulation, and inflammatory signaling.[51] Although much of the current evidence derives from experimental models, the mechanistic plausibility of pharmacokinetic alteration is increasingly supported by emerging data.[52] **Figure 1** & **2** illustrate mechanistic pathways by which microplastics (MPs) and nanoplastics (NPs) may alter human drug pharmacokinetics, and the potential influence of MPs/NPs on the four major components of pharmacokinetics, respectively.

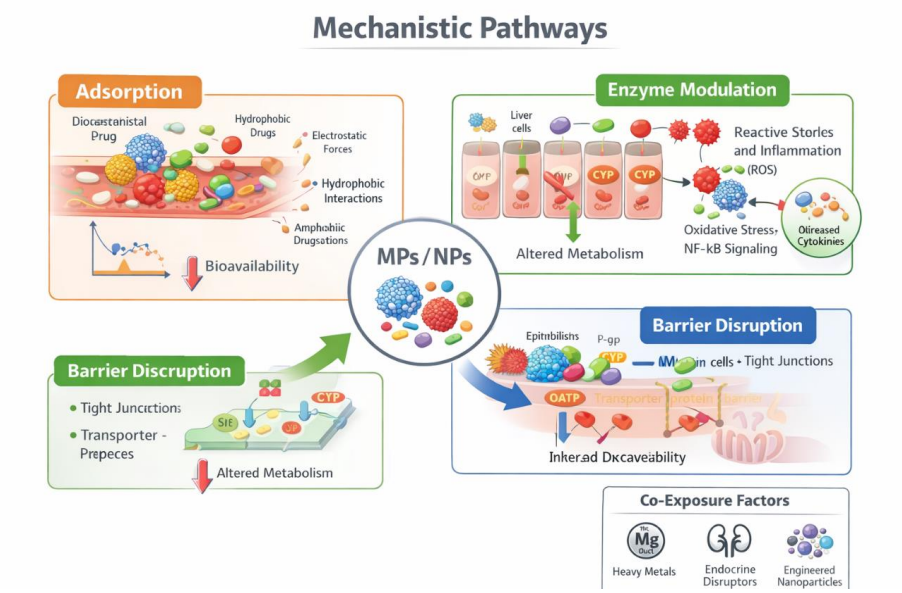

Figure 1: Mechanistic pathways by which microplastics (MPs) and nanoplastics (NPs) may alter human drug pharmacokinetics.

2.1 Absorption

Interaction in the Gastrointestinal Tract

The gastrointestinal tract represents the primary site of both oral drug administration and environmental microplastic exposure. Within the intestinal lumen, MPs and NPs coexist with bile salts, digestive enzymes, dietary lipids, and microbiota, creating a complex chemical environment.[53] Plastic particles may interact directly with administered drugs before epithelial absorption occurs.[54] Factors such as luminal pH, ionic strength, and the presence of food components influence the stability and aggregation behavior of particles, which in turn affects drug–particle interactions.[55]

Adsorption of Drugs onto MPs/NPs

Due to their hydrophobic surfaces and high surface-area-to-volume ratios, MPs and especially NPs can adsorb pharmaceutical compounds through hydrophobic partitioning, electrostatic attraction, hydrogen bonding, and π–π interactions.[56] Lipophilic drugs are particularly susceptible to partitioning onto polymer surfaces.[57] This adsorption may reduce the fraction of free drug available for passive diffusion across the intestinal epithelium, potentially lowering bioavailability.[58]

Conversely, particles may act as secondary carriers. Adsorbed drugs could desorb gradually at the epithelial surface, prolonging local exposure and altering time to peak concentration.[59]

The balance between sequestration and delayed release depends on binding affinity, particle concentration, and luminal transit time.[60]

Effects on Intestinal Permeability

Experimental studies have shown that NPs can disrupt tight junction proteins, induce epithelial oxidative stress, and compromise barrier integrity.[61] Increased paracellular permeability may enhance the absorption of certain hydrophilic drugs. However, chronic epithelial damage or inflammation may also impair absorptive surface area and reduce transporter function.[62] The net effect on drug absorption is therefore context-dependent and may vary according to exposure duration and particle characteristics.

Impact on Transporters (P-gp, OATP, BCRP)

Drug transporters such as P-glycoprotein (P-gp), organic anion transporting polypeptides (OATPs), and breast cancer resistance protein (BCRP) play central roles in regulating intestinal drug uptake and efflux.[63] Evidence suggests that MPs and NPs can modulate transporter expression through oxidative stress and inflammatory signaling pathways.[64] Upregulation of efflux transporters may decrease intracellular drug accumulation, whereas downregulation could increase systemic exposure and toxicity risk.[65] These alterations are particularly relevant for drugs with narrow therapeutic indices or strong transporter dependence.

Influence on Gut Microbiota

The gut microbiota contributes to drug metabolism, enterohepatic cycling, and regulation of host enzyme expression. MPs and NPs have been associated with dysbiosis, altered microbial diversity, and increased pro-inflammatory species in experimental models.[66] Microbiota disruption may indirectly modify the biotransformation of drugs such as antibiotics, immunosuppressants, and certain cardiovascular agents.[67] Changes in microbial enzyme activity can influence drug activation, deactivation, or formation of toxic metabolites.

2.2 Distribution

Translocation Across Epithelial Barriers

Nanoplastics are capable of translocating across intestinal epithelium into systemic circulation via endocytosis or M-cell–mediated transport.[68] Once in the bloodstream, they may serve as carriers for adsorbed drugs, altering distribution kinetics. Particle-bound drugs

may exhibit delayed tissue uptake or redistribution depending on desorption dynamics and vascular permeability.[69]

Blood–Brain Barrier Penetration

Experimental evidence indicates that very small NPs can cross the blood–brain barrier (BBB), particularly under conditions of inflammation or oxidative stress.[70] If drug molecules remain adsorbed during translocation, NPs could theoretically facilitate central nervous system exposure.[71] Alternatively, particle-induced BBB disruption might increase permeability to free drug molecules, potentially enhancing neurotoxicity or therapeutic effect.[72]

Interaction with Plasma Proteins

In circulation, MPs and NPs rapidly acquire a protein corona composed of albumin, immunoglobulins, apolipoproteins, and other plasma constituents.[73] This corona may compete with drugs for protein-binding sites or alter the free fraction of highly protein-bound medications.[74] Changes in plasma protein binding can significantly affect distribution volume and pharmacodynamic response.[75]

Tissue Accumulation and Drug Redistribution

Plastic particles have been detected in liver, spleen, lung, kidney, and placental tissue in experimental models.[76] Accumulation within reticuloendothelial organs may influence local drug concentrations, either by sequestration or by modifying local inflammatory and metabolic environments.[77] Tissue-level redistribution may contribute to altered efficacy or organ-specific toxicity.

2.3 Metabolism

Modulation of Hepatic Enzymes (CYP450 Isoforms)

The liver is a primary target for both drug metabolism and microplastic accumulation.[78] Experimental studies suggest that exposure to MPs and NPs can alter the expression and activity of cytochrome P450 enzymes, including CYP3A, CYP2C, and CYP1A isoforms.[79] Such modulation may lead to altered intrinsic clearance and unpredictable systemic exposure.

Oxidative Stress–Mediated Enzyme Alteration

Plastic particle exposure frequently induces reactive oxygen species production and mitochondrial dysfunction.[80] Oxidative stress can downregulate certain metabolic enzymes

or shift metabolic pathways toward alternative routes.[81] These changes may influence the formation of active or toxic metabolites, particularly for drugs requiring metabolic activation.[82]

Inflammatory Signaling and Metabolic Changes

Inflammatory mediators such as tumor necrosis factor-α and interleukins are upregulated in response to particle exposure in various models.[83] Chronic inflammation can suppress hepatic enzyme expression and alter phase II conjugation pathways.[84] This systemic response may indirectly modify drug metabolism beyond direct hepatocellular effects.

Evidence from In Vivo and In Vitro Models

Cell culture studies using hepatocyte and intestinal models demonstrate altered enzyme activity following NP exposure.[85] Animal studies report changes in hepatic enzyme expression and modified pharmacokinetic profiles for selected compounds.[86] However, translation to human exposure scenarios remains limited, highlighting the need for integrated pharmacokinetic investigations.

2.4 Excretion

Renal Tubular Interaction

Kidney accumulation of plastic particles has been observed in animal studies. Tubular epithelial injury, oxidative stress, and inflammatory infiltration may impair active secretion and reabsorption mechanisms.[87] Drugs eliminated primarily through renal pathways may therefore exhibit prolonged half-life or altered clearance.

Hepatobiliary Clearance

Inflammatory or structural changes in hepatocytes and bile canaliculi may disrupt biliary excretion of drugs and metabolites. Additionally, interference with transporters involved in bile secretion could alter enterohepatic recirculation patterns.[88]

Alteration of Drug Elimination Kinetics

Combined effects on metabolism and excretion may lead to measurable changes in elimination rate constants, half-life, and systemic exposure. Depending on the direction of modulation, MPs and NPs may increase toxicity risk or reduce therapeutic efficacy.[7] The magnitude of these changes is likely influenced by chronic exposure level, particle characteristics, and patient-specific factors.

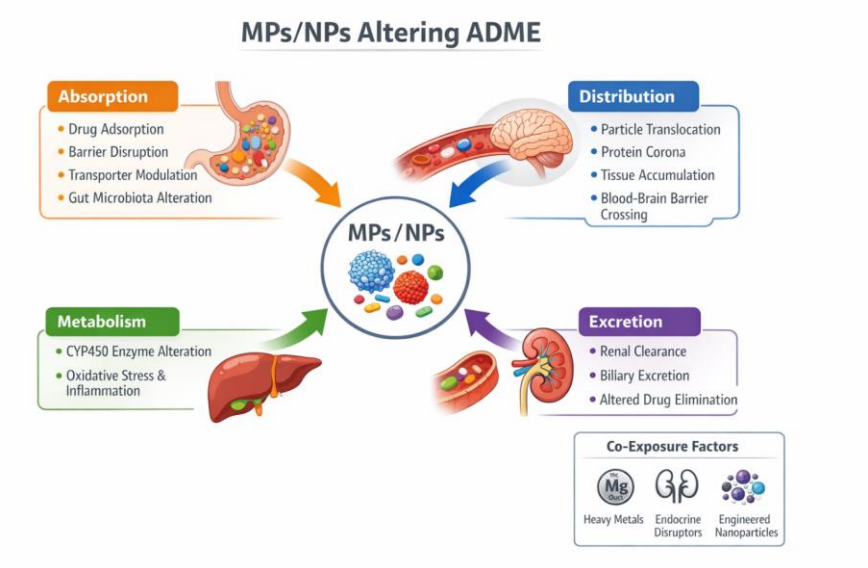

Figure 2: Impact of microplastics (MPs) and nanoplastics (NPs) on human ADME processes.

3. Pharmacokinetic Modeling Considerations

The potential influence of microplastics (MPs) and nanoplastics (NPs) on drug disposition introduces new challenges for pharmacokinetic modeling. Traditional pharmacokinetic frameworks assume predictable absorption, distribution, metabolism, and excretion processes governed primarily by physiological parameters and drug-specific properties. However, if environmental particles act as dynamic sorptive matrices, barrier modulators, or enzyme regulators, conventional models may underestimate variability in systemic exposure. Incorporating particle-related parameters into pharmacokinetic simulations is therefore essential to evaluate clinical relevance and risk.

Impact on Bioavailability

Bioavailability reflects the fraction of an administered dose that reaches systemic circulation in an active form. MPs and NPs may alter oral bioavailability through two opposing mechanisms. First, luminal adsorption of drug molecules onto particle surfaces may reduce the free fraction available for epithelial absorption, effectively lowering apparent bioavailability.[89] This effect would be particularly relevant for lipophilic drugs with high affinity for hydrophobic polymer surfaces.

Second, if particles act as transient carriers that release adsorbed drug near the epithelial surface, they may prolong local exposure and potentially enhance absorption for certain compounds.[90] Additionally, particle-induced changes in intestinal permeability or transporter

expression may modify the fraction absorbed (Fa) and first-pass extraction (Fg).[91] These competing influences suggest that net bioavailability changes are drug-specific and dependent on particle concentration, binding affinity, and exposure duration.

Modeling these interactions requires incorporation of an additional binding equilibrium in the gastrointestinal compartment. The fraction of drug reversibly bound to particles can be represented using association and dissociation constants, allowing simulation of dynamic sequestration and release.

Changes in C_{max}, T_{max}, and AUC

Alterations in absorption kinetics and systemic clearance are expected to affect key pharmacokinetic parameters. A reduction in free drug absorption may decrease maximum plasma concentration (C_{max}) and area under the concentration–time curve (AUC).[92] Conversely, delayed desorption from particles may shift time to peak concentration (Tmax) and prolong apparent absorption phases.[93]

If particle exposure modifies metabolic enzyme activity or renal clearance, elimination rate constants may change, further influencing AUC and half-life.[94] For drugs with narrow therapeutic indices, even modest shifts in C_{max} or AUC could have clinical consequences.[95] Therefore, modeling scenarios should evaluate both acute co-exposure and chronic environmental exposure conditions to assess cumulative impact on steady-state concentrations.

Sensitivity analyses can help determine which parameters most strongly influence predicted changes. For example, simulations may vary particle concentration, binding affinity, or degree of enzyme modulation to identify threshold conditions under which clinically meaningful differences emerge.[96]

Compartmental vs Physiologically Based Pharmacokinetic (PBPK) Models

Traditional compartmental models, including one- and two-compartment frameworks, provide simplified mathematical representations of drug distribution and elimination.[97] While useful for identifying empirical changes in C_{max}, T_{max}, or clearance, they ck mechanistic detai regarding tissue-specific interactions.[98] Incorporating particle effects into such models typically involves adding modified absorption rate constants, altered clearance terms, or additional binding compartments.

In contrast, physiologically based pharmacokinetic (PBPK) models offer a more suitable platform for integrating microplastic-related variables. PBPK models represent organs and tissues as discrete compartments connected by blood flow, with parameters reflecting physiological and biochemical processes.[99] Particle–drug interactions can be incorporated at specific sites, such as the intestinal lumen, hepatic tissue, or renal tubules.[100]

For example, a PBPK framework may include

- A luminal sub-compartment representing reversible drug binding to particles
- Modified intestinal permeability coefficients reflecting barrier disruption
- Enzyme activity scaling factors in the liver to simulate CYP modulation
- Adjusted renal secretion parameters to account for tubular effects.[101,102]

This mechanistic structure allows exploration of different exposure scenarios, including chronic low-dose environmental exposure or high acute co-exposure.[103] It also facilitates extrapolation from animal data to humans by scaling physiological parameters.

Incorporation of Particle–Drug Binding Constants

A critical step in quantitative modeling is the integration of particle–drug binding constants. These parameters describe the affinity and capacity of MPs and NPs to adsorb specific drugs.[104] Binding can be modeled using linear partition coefficients for low-affinity interactions or nonlinear isotherms, such as Langmuir or Freundlich models, for saturable adsorption.[105]

In the gastrointestinal compartment, the free drug concentration (C_f) can be expressed as a function of total drug concentration (C_t), particle concentration (P), and binding constant (K_d). This relationship enables prediction of the fraction of drug temporarily sequestered on particle surfaces.[106] Time-dependent desorption rates should also be considered, particularly for drugs with slow-release kinetics.

In systemic circulation, similar binding parameters may be applied if particle translocation occurs. However, modeling must account for the formation of a protein corona, which may alter effective binding affinity and introduce competitive interactions with plasma proteins.[107]

4. Experimental Evidence

Although the concept of microplastics (MPs) and nanoplastics (NPs) as modifiers of drug pharmacokinetics is still emerging, a growing body of experimental research provides mechanistic support. Most available data originate from toxicological investigations rather than dedicated pharmacokinetic interaction studies. Nevertheless, findings from in vitro systems, animal models, and early human biomonitoring studies collectively suggest plausible pathways through which MPs and NPs may influence drug disposition. **Table 2** provides an overview of in vitro, in vivo, and human studies investigating how MPs/NPs may modify drug pharmacokinetics

4.1 In Vitro Studies

Cell Line Models (Caco-2, HepG2, etc.)

In vitro models have been instrumental in elucidating cellular responses to plastic particle exposure. Human intestinal epithelial cell lines such as Caco-2 are widely used to simulate the absorptive barrier of the small intestine.[108] Exposure to polystyrene or polyethylene nanoplastics in Caco-2 monolayers has been associated with altered tight junction protein expression, increased oxidative stress, and changes in transepithelial electrical resistance.[109] These findings indicate potential modulation of paracellular permeability, which may influence the absorption of orally administered drugs.

HepG2 hepatocyte-derived cells provide insight into hepatic metabolic responses. Studies report that NP exposure can induce reactive oxygen species generation, mitochondrial dysfunction, and altered expression of cytochrome P450 enzymes.[110,111] Downregulation or dysregulation of CYP isoforms suggests possible changes in intrinsic metabolic clearance.[112] Although these experiments often assess toxicological endpoints rather than drug-specific kinetics, they highlight biologically relevant mechanisms that may modify drug metabolism.[113]

Macrophage and endothelial cell models further demonstrate particle uptake, inflammatory cytokine release, and altered membrane transport activity.[113] These cellular responses are relevant to systemic distribution and tissue-specific accumulation.

Transport and Enzyme Assays

Transporter assays have shown that particle exposure can influence the expression and activity of key efflux and uptake transporters, including P-glycoprotein (P-gp) and organic

anion transporting polypeptides.[14,114] Changes in transporter activity may affect intracellular drug accumulation and directional flux across epithelial barriers.

Enzyme activity assays, particularly those evaluating CYP450-mediated metabolism, reveal variable responses depending on particle size, concentration, and surface functionalization. Some studies report suppression of metabolic activity linked to oxidative stress, while others observe compensatory upregulation.[115] Importantly, these changes often occur at particle concentrations higher than typical environmental exposure levels, raising questions about real-world relevance.[116]

Overall, in vitro studies provide mechanistic plausibility but remain limited by simplified exposure conditions, absence of whole-organism physiology, and lack of direct drug–particle co-exposure assessments in many cases.

4.2 In Vivo Animal Studies

Rodent Exposure Models

Rodent models have been widely employed to evaluate systemic distribution and organ-specific toxicity following oral or inhalational exposure to MPs and NPs. After chronic exposure, particles have been detected in liver, kidney, spleen, lung, brain, and reproductive tissues. Histopathological findings frequently include inflammatory infiltration, oxidative stress markers, and mild structural alterations.[117]

Hepatic accumulation is particularly relevant for drug metabolism. Studies in exposed rodents demonstrate altered expression of metabolic enzymes and inflammatory mediators in liver tissue.[117] Similarly, renal accumulation has been associated with tubular injury and oxidative stress, suggesting potential effects on drug elimination pathways.[87]

Although most animal experiments do not administer pharmaceutical agents concurrently, some preliminary investigations have reported altered pharmacokinetic profiles of co-administered compounds. Changes in plasma concentration–time curves, tissue distribution patterns, and elimination rates have been observed, supporting the hypothesis that particle exposure can modify systemic drug handling.[118]

Changes in Drug Levels and Tissue Distribution

In experimental co-exposure scenarios, adsorptive interactions between drugs and particles may alter absorption efficiency.[69] Additionally, sstemic inflammation induced by particle

exposure may modify hepatic clearance or renal excretion, indirectly affecting circulating drug levels.[88] Tissue redistribution of particles may also create localized environments that influence drug accumulation or toxicity.[119]

However, interpretation of animal data requires caution. Exposure concentrations are often higher than those estimated for human populations, and differences in species-specific metabolism limit direct extrapolation. Nonetheless, rodent studies offer valuable insights into integrated physiological responses that cannot be captured in vitro.

4.3 Human Evidence

Biomonitoring Data

Human studies have confirmed the presence of microplastic particles in stool, blood, placenta, lung tissue, and other biological samples.[76] These findings demonstrate that systemic exposure and translocation are possible. However, direct measurement of drug–particle interactions in human subjects remains scarce.

Biomonitoring efforts primarily focus on particle detection rather than pharmacokinetic outcomes. The lack of longitudinal data linking particle burden with medication response represents a significant knowledge gap.

Indirect Epidemiological Correlations

Some epidemiological observations suggest associations between environmental pollution exposure and altered drug efficacy or disease progression.[120] While these correlations are not specific to microplastics, they raise the possibility that environmental co-exposures may influence therapeutic outcomes. For instance, populations with high environmental contaminant exposure sometimes exhibit variable responses to pharmacotherapy, though causal mechanisms remain unclear.[121]

Currently, no large-scale clinical studies have directly examined whether measured microplastic burden correlates with changes in C_{max}, AUC, clearance, or therapeutic response for specific medications.

Current Limitations

Human evidence is limited by methodological challenges in particle detection, variability in exposure assessment, and absence of standardized quantification protocols. Furthermore,

most studies lack simultaneous measurement of pharmacokinetic parameters. Ethical constraints also complicate controlled exposure research.

Consequently, while experimental models provide mechanistic insight, translation to clinical practice remains preliminary. Future research must integrate biomonitoring with pharmacokinetic profiling, ideally using physiologically based models to bridge experimental and human data.

Table 2: Summary of Experimental Evidence.

Study Type	Model /Species	Exposure / Particle	Key Findings on ADME	Ref
In Vitro	Caco-2, HepG2	Polystyrene NPs	Altered tight junctions, reduced absorption, CYP450 modulation	[122]
In Vitro	Macrophages, endothelial cells	PE, PS NPs	Increased oxidative stress, cytokine release, transporter modulation	[19,123]
In Vivo	Rodents (mice/rats)	Oral/inhalation MPs/NPs	Tissue accumulation (liver, kidney, spleen, brain), altered drug clearance, plasma concentration changes	[124,125]
Human	Biomonitoring	MPs in blood, stool, placenta	Systemic exposure confirmed; direct pharmacokinetic data limited, indirect associations with drug response	[126,127]

5. Therapeutic and Clinical Implications

If microplastics (MPs) and nanoplastics (NPs) meaningfully alter drug pharmacokinetics, the consequences extend beyond theoretical modeling and into clinical practice. Even modest changes in absorption, distribution, metabolism, or excretion can influence therapeutic response, particularly for drugs with tight exposure–response relationships. While direct human evidence remains limited, mechanistic and experimental findings raise important considerations for efficacy, safety, and patient-specific vulnerability. **Table 3.** links mechanistic vulnerabilities of different drug classes to possible clinical outcomes when co-exposed to MPs/NPs.

Reduced Drug Efficacy

One potential outcome of particle–drug interaction is reduced therapeutic effectiveness. Adsorption of drug molecules onto MPs or NPs in the gastrointestinal tract may lower the fraction of free drug available for absorption, thereby decreasing systemic exposure.[128]

Reduced bioavailability could lead to subtherapeutic plasma concentrations, delayed onset of action, or incomplete clinical response.[129]

Alterations in intestinal transporter expression or enhanced efflux activity may further limit intracellular drug accumulation.[130] Similarly, upregulation of hepatic metabolic enzymes could accelerate clearance, shortening half-life and lowering steady-state concentrations.[131] For chronic therapies such as antihypertensives, antidiabetics, or antidepressants, subtle reductions in systemic exposure might compromise long-term disease control without immediately obvious clinical signs.[69]

In addition, disruption of gut microbiota by chronic particle exposure may interfere with drugs that rely on microbial metabolism for activation or enterohepatic recirculation.[132] This indirect pathway could contribute to variability in treatment outcomes across populations with differing environmental exposure burdens.

Increased Toxicity Risk

In contrast to reduced efficacy, certain mechanisms may increase systemic exposure and heighten toxicity risk. Downregulation of metabolic enzymes or impairment of renal elimination pathways could elevate plasma drug concentrations beyond intended therapeutic ranges.[132] Similarly, disruption of plasma protein binding equilibria may increase the free fraction of highly protein-bound drugs, enhancing pharmacodynamic effect and adverse event potential.[133]

Particle-induced epithelial barrier dysfunction may also increase intestinal permeability, facilitating higher-than-expected absorption of certain compounds.[134] If nanoplastics cros the blood–brain barrier or alter its integrity, central nervous system exposure to neuroactive drugs could be amplified.[135] These scenarios are particularly concerning for medications associated with dose-dependent toxicity.

The risk is further compounded by chronic inflammatory responses induced by particle exposure. Inflammation itself can suppress hepatic enzyme activity and alter transporter function, creating a systemic milieu that modifies drug handling independent of direct adsorption effects.[136]

Narrow Therapeutic Index Drugs

Drugs with narrow therapeutic indices are especially susceptible to small pharmacokinetic perturbations. Antiepileptics such as phenytoin or carbamazepine require careful monitoring due to nonlinear metabolism and dose-dependent toxicity. Even minor changes in clearance could precipitate seizure recurrence or adverse neurological effects.[137]

Similarly, anticoagulants such as warfarin or direct oral anticoagulants depend on stable systemic exposure to maintain efficacy while avoiding bleeding complications.[138] Variability in absorption or hepatic metabolism could shift patients outside the therapeutic window. Immunosuppressants, certain chemotherapeutic agents, and cardiac glycosides represent additional high-risk categories.[139]

For such medications, environmental modifiers of pharmacokinetics may contribute to unexplained variability in plasma concentrations or treatment response. Although routine clinical practice does not currently account for microplastic exposure, future precision medicine approaches may need to consider environmental co-exposures as part of individualized risk assessment.

Vulnerable Populations

Certain groups may be disproportionately affected by particle-mediated pharmacokinetic alterations. Pregnant women represent a critical population, as microplastics have been detected in placental tissue.[140] Altered maternal drug disposition could influence both maternal therapy and fetal exposure.[141] Inflammatory or oxidative stress responses during pregnancy may further modify enzyme expression and transporter activity.[142]

Older adults are another vulnerable group. Age-related reductions in renal and hepatic function already increase pharmacokinetic variability.[143] Superimposed environmental particle exposure may exacerbate these changes, particularly in patients receiving polypharmacy.[144]

Patients with chronic diseases, including liver disease, kidney impairment, inflammatory bowel disease, or metabolic disorders, may also exhibit heightened susceptibility.[145] Pre-existing barrier dysfunction or impaired clearance mechanisms could amplify the impact of particle-induced changes.[146] Moreover, individuals living in regions with high

environmental plastic contamination may experience cumulative exposure that interacts with long-term pharmacotherapy.[147]

Table 3: Potential Clinical Consequences by Drug Class.

Drug Class	Mechanistic Vulnerability	Potential Clinical Implications	Ref.
Antiepileptics	Narrow therapeutic index, CYP450 metabolism	Reduced efficacy or toxicity due to altered metabolism/absorption	[148]
Anticoagulants (e.g., warfarin)	Highly protein-bound, metabolism-sensitive	Bleeding or subtherapeutic effect from altered plasma concentrations	[149]
Biologics (monoclonal antibodies, peptides)	Susceptible to adsorption and protein corona effects	Reduced bioavailability, altered tissue distribution	[150]
Nanomedicine / Liposomal Drugs	Competition with environmental NPs	Reduced targeting efficiency, altered release kinetics	[151]
Cardiovascular Drugs	CYP450-mediated metabolism	Unstable plasma levels, risk of adverse cardiovascular events	[152]
Anticancer Drugs	Narrow therapeutic index, hepatic metabolism	Potential toxicity or decreased antitumor efficacy	[153]

6. Special Considerations

Beyond conventional small-molecule drugs, microplastics (MPs) and nanoplastics (NPs) may influence more complex therapeutic systems, including biologics, advanced drug delivery platforms, and multi-pollutant environments. These interactions introduce additional layers of pharmacokinetic and pharmacodynamic complexity that are important to consider in both clinical and research contexts.

6.1 Interaction with Biologics

Biologics, including monoclonal antibodies, peptide therapeutics, and nucleic acid-based drugs, have distinct pharmacokinetic profiles compared to small molecules.[154] Their absorption, distribution, and clearance are highly sensitive to protein binding, enzymatic degradation, and endocytosis pathways.[155] MPs and NPs can adsorb proteins or peptides on their surfaces, potentially sequestering biologics in the gastrointestinal lumen or altering systemic distribution if particles translocate into circulation.[53]

Moreover, the protein corona formed around NPs in plasma could compete with biologics for binding sites, potentially modifying half-life or biodistribution.[50] Inflammatory responses triggered by particle exposure may also alter the expression of Fc receptors or proteolytic enzymes involved in biologic metabolism, indirectly affecting drug clearance.[156] These mechanisms suggest that biologic therapies may be particularly sensitive to environmental particle exposure, warranting consideration in high-risk populations or regions with elevated microplastic contamination.

6.2 Nanomedicine and Drug Delivery Systems

Engineered nanoparticles, liposomes, and polymeric drug delivery systems are increasingly used to enhance targeted delivery, improve solubility, or extend circulation time.[157] The presence of environmental MPs or NPs introduces a potential for competitive or interference effects.[158] Adsorptive interactions may sequester therapeutic nanoparticles, reducing their effective concentration at target sites.[73] Additionally, particle-induced modulation of transporters, barrier integrity, or immune clearance could alter the distribution and clearance of engineered nanoparticles, undermining controlled release or targeting efficiency.[159]

Protein corona formation is particularly relevant in this context. Both therapeutic and environmental particles acquire coronas in plasma, which may modify immune recognition, aggregation, and tissue accumulation.[160] These interactions could compromise nanomedicine efficacy, safety, or reproducibility, emphasizing the need for careful evaluation in preclinical models that account for environmental particle exposure.

6.3 Co-exposure with Environmental Pollutants

Human exposure to MPs and NPs rarely occurs in isolation. Co-exposure with other environmental contaminants, such as heavy metals and endocrine-disrupting chemicals, is common and may amplify pharmacokinetic and pharmacodynamic effects.[161] Microplastics can act as vectors for adsorbed pollutants, increasing local concentrations in the gastrointestinal tract or systemic circulation.[162]

Heavy metals such as cadmium, lead, and mercury can bind to particle surfaces and influence oxidative stress, renal function, and hepatic enzyme activity.[163] This may compound particle-mediated alterations in drug metabolism and excretion. Similarly, endocrine-disrupting chemicals can interfere with hormone-dependent drug transporters, cytochrome

P450 enzymes, or nuclear receptor signaling, creating additional variability in therapeutic outcomes.[164]

Such combined exposures may produce additive or synergistic effects, complicating predictions based on single-particle models. Understanding co-exposure dynamics is essential for realistic risk assessment and may help explain interindividual variability in drug response observed in populations exposed to environmental contaminants.

7. Regulatory and Public Health Perspectives

The emergence of microplastics (MPs) and nanoplastics (NPs) as potential modifiers of drug pharmacokinetics exposes significant gaps in current regulatory frameworks. Existing guidelines for drug safety assessment and environmental toxicology rarely consider particle-mediated interactions with pharmaceuticals.[165] Standard preclinical and clinical testing protocols do not routinely incorporate environmental co-exposures, nor do they evaluate the potential for microplastics to alter absorption, metabolism, or clearance of therapeutic agents.[166]

This gap highlights the need for integration of environmental health considerations into pharmacology and drug evaluation. Regulatory agencies may need to develop guidance on assessing particle–drug interactions, particularly for high-risk compounds such as narrow therapeutic index drugs, biologics, and nanomedicines.[167] Risk assessment strategies could include standardized testing of particle adsorption, transporter modulation, enzyme activity, and systemic translocation under environmentally relevant exposure conditions.[168]

From a public health perspective, widespread environmental contamination with MPs and NPs poses potential population-level risks. Chronic low-level exposure may contribute to interindividual variability in therapeutic outcomes, with disproportionate effects on vulnerable populations including pregnant women, the elderly, and patients with chronic disease. Surveillance programs and environmental monitoring could help identify exposure hotspots, while pharmacovigilance systems might integrate environmental co-exposure data to inform clinical guidelines and drug dosing recommendations.[169]

8. Research Gaps and Future Directions

Despite growing mechanistic evidence, critical research gaps remain. First, standardized exposure models are needed to replicate environmentally relevant concentrations, particle

types, sizes, and surface modifications. Most current studies use supraphysiological doses, limiting translational applicability. Second, long-term human pharmacokinetic studies are essential. Biomonitoring combined with drug plasma profiling could clarify whether chronic exposure meaningfully alters therapeutic outcomes. Observational studies may provide preliminary insights, but controlled investigations will be required to establish causality. Third, integration with physiologically based pharmacokinetic (PBPK) modeling offers a pathway to mechanistically link experimental data with human pharmacokinetics. Incorporating particle–drug binding constants, transporter modulation, and enzyme alteration into PBPK models can help predict systemic exposure and guide risk assessment. Fourth, multi-omics approaches—including transcriptomics, proteomics, and metabolomics—can elucidate the molecular and systemic responses to particle exposure, revealing interactions that influence drug metabolism, transport, and distribution. Finally, interdisciplinary collaboration is critical. Bridging environmental science, toxicology, pharmacology, and clinical medicine will enable holistic understanding of particle-mediated pharmacokinetic effects and inform regulatory strategies, risk assessment, and patient care.

DISCUSSION

Microplastics (MPs) and nanoplastics (NPs) are increasingly recognized as environmental contaminants with the potential to influence human drug pharmacokinetics.[170] Their unique physicochemical characteristics—including particle size, surface area, polymer type, surface charge, and functionalization—determine their interaction with therapeutic compounds and biological systems.[8] Nanoplastics, with diameters typically below 100 nm, present high surface-area-to-volume ratios that facilitate adsorption of drugs, particularly hydrophobic or amphiphilic molecules.[171] Surface charge influences interactions with epithelial surfaces, intestinal mucus, and plasma proteins, while surface functionalization or aging alters binding affinities and protein corona formation.[32] Collectively, these properties suggest that MPs/NPs can modify absorption, distribution, metabolism, and excretion (ADME) in ways that may impact drug efficacy and safety.

Experimental evidence from in vitro studies supports mechanistic plausibility. Intestinal epithelial cell models (e.g., Caco-2) show that MPs/NPs can disrupt tight junctions, modulate paracellular transport, and alter the activity of drug transporters such as P-glycoprotein, OATP, and BCRP.[108] Hepatic cell lines (HepG2) demonstrate changes in CYP450 enzyme expression and oxidative stress–mediated modulation of metabolic pathways.[172]

Macrophage and endothelial models further indicate inflammatory responses, particle uptake, and altered intracellular transport.[173] These findings suggest that MPs/NPs can simultaneously affect absorption, metabolism, and systemic distribution at the cellular level.

In vivo rodent studies corroborate these findings. Chronic oral or inhalational exposure leads to accumulation in liver, kidney, spleen, and brain, accompanied by mild histopathological changes and oxidative stress.[174] Altered expression of metabolic enzymes and transporters has been reported, with evidence of changes in plasma drug concentrations and tissue distribution when co-exposed to therapeutic compounds.[175] Although most studies used particle doses higher than environmental exposure levels, they highlight physiologically relevant pathways for drug–particle interactions and support the possibility of systemic effects in humans.

Human data are more limited, consisting primarily of biomonitoring studies detecting MPs in stool, blood, and placental tissue.[176] While direct pharmacokinetic consequences remain unquantified, these studies confirm that systemic exposure occurs. Co-exposure with other environmental pollutants, such as heavy metals and endocrine disruptors, may amplify particle-mediated effects, potentially altering drug metabolism, clearance, or tissue distribution.[177]

The clinical implications of these findings are particularly significant for drugs with narrow therapeutic indices. Antiepileptics, anticoagulants, biologics, and nanomedicine formulations are susceptible to small changes in absorption, metabolism, or protein binding.[178,179] Reduced efficacy or enhanced toxicity could arise from adsorption of drugs onto particles, altered transporter activity, or enzyme modulation.[180] Vulnerable populations, including pregnant women, the elderly, and patients with chronic disease, may experience heightened risk due to pre-existing physiological susceptibilities.[181]

Regulatory frameworks currently do not account for particle-mediated drug interactions. Standard preclinical and clinical testing does not evaluate environmental co-exposure or particle–drug interactions, highlighting a critical gap in drug safety assessment.[182] Addressing this will require the integration of physiologically based pharmacokinetic (PBPK) modeling, standardized particle exposure models, and long-term human pharmacokinetic studies.[183] Multi-omics approaches may provide mechanistic insights into systemic responses, including inflammation, oxidative stress, and transporter or enzyme modulation. Interdisciplinary collaboration among environmental scientists, pharmacologists, and

clinicians will be essential to evaluate clinical relevance, guide regulatory policies, and develop mitigation strategies.[184]

In summary, MPs and NPs represent an emerging class of environmental modifiers capable of altering drug pharmacokinetics through adsorption, barrier disruption, and enzyme modulation. Experimental evidence supports biologically plausible mechanisms, while clinical and regulatory implications underscore the need for focused research. Recognizing the influence of environmental plastics on drug disposition is essential for precision pharmacotherapy, patient safety, and public health. Addressing these challenges will require coordinated research efforts to bridge environmental exposure science with pharmacology and clinical practice.

CONCLUSION

Microplastics and nanoplastics represent an emerging class of environmental modifiers with the potential to influence every phase of drug pharmacokinetics. Mechanistically, they may alter absorption through luminal adsorption and barrier modulation, redistribute drugs via systemic translocation, modulate hepatic and intestinal enzyme activity, and affect renal and biliary excretion. Special considerations include interactions with biologics, engineered nanoparticles, and co-exposure to other environmental pollutants.

These mechanistic insights carry important clinical implications, particularly for drugs with narrow therapeutic indices, vulnerable patient populations, and advanced delivery systems. Current regulatory frameworks and drug safety evaluations do not yet account for these interactions, underscoring the need for integration of environmental–pharmacology perspectives.

Urgent research is needed to quantify real-world impacts, standardize exposure models, and bridge experimental findings with human pharmacokinetics. Multi-omics investigations, PBPK modeling, and interdisciplinary approaches will be essential to fully understand and mitigate the potential effects of environmental plastic contamination on therapeutic outcomes. Recognition of microplastics and nanoplastics as modulators of drug disposition represents a new frontier at the intersection of environmental health and clinical pharmacology.

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Competing Interests

None.

Authors' contributions

Md. Al Amin conceptualized the study, conducted the literature search, synthesized the evidence, drafted the manuscript, and correspondence. **Dr. Md. Mofazzal Hossain** supervised the work, contributed to critical revision for important intellectual content, and provided overall guidance. Both authors reviewed, edited, and approved the final version of the manuscript.

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