

Organ-on-Chip-Guided Evaluation of Nanocarrier Transport Across Biological Barriers: A Critical Review of Predictive Models for Translational Drug Delivery

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Abstract

Drug delivery systems based on nanocarriers can cross biological barriers to regulate the movement of molecules and particles between different physiological compartments, which plays an important role in therapeutic performance. Two-dimensional cell cultures and animal models are important sources of preclinical information but often do not replicate the dynamic mechanical, cellular, and structural properties that dictate nanocarrier transport in humans. Organ-on-chip systems are sophisticated microphysiological systems that can mimic tissue interfaces in a controlled environment with fluid flow, shear stress, multicellular structure, and extracellular matrix. These systems offer novel possibilities to study permeability, cellular uptake, transcytosis, barrier accumulation, and barrier-associated toxicity of nanocarriers in physiologically relevant environments. This review critically summarizes organ-on-chip studies on the transport of nanocarriers across key biological barriers such as the blood-brain, intestinal, pulmonary, placental, vascular/tumor, renal, and skin barriers. Specific focus is given to the physicochemical factors that influence the transport of nanocarriers, the quantitative evaluation of barriers, predictive performance, and translational relevance. The use of organ-on-chip information in physiologically based pharmacokinetic modelling, in-vitro-in-vivo extrapolation and with the development of artificial intelligence is also addressed. Despite the standardization, reproducibility and material selection, scaling and validation hurdles, organ-on-chip technology seems to be a bridge between experimental nanomedicine and drug-delivery prediction in humans.

Keywords: Organ-on-chip; Nanocarriers; Biological barriers; Drug delivery; Microfluidics; Nanoparticles; Translational models

How to cite this article: Nicky Kumar Jaiswal* Shubham¹ Mohd Afsar² Madhu Bala³ Manpreet Kaur Deol⁴ Deepak kumar jha⁵ Swati Kaushal⁶ Anshkumar Bhuva⁷ Km Priyanka Singh⁸. Organ-on-Chip-Guided Evaluation of Nanocarrier Transport Across Biological Barriers: A Critical Review of Predictive Models for Translational Drug Delivery. Int J Drug Deliv Technol. 2026;16(85s):1155-1166. DOI: 10.25258/ijddt.16.85s.121.

1. Introduction

Biological barriers maintain tissue homeostasis by tightly controlling the movement of endogenous molecules, xenobiotics, microorganisms, and therapeutic agents between physiological compartments. Although these barriers are essential for normal organ function, they also represent major obstacles to effective drug delivery. The blood-brain barrier, intestinal mucosa, pulmonary epithelium, placental interface, skin, renal filtration system, and

tumor-associated vasculature possess distinct structural and biochemical properties that can substantially restrict therapeutic penetration. Nanocarriers have consequently been developed to improve drug solubility, protect unstable therapeutic cargo, modify pharmacokinetic behaviour, and enhance site-specific delivery. However, the biological performance of nanoscale delivery systems remains highly dependent on their interactions with

complex physiological barriers, and promising preclinical formulations do not always show equivalent behaviour in humans [1,2].

The development of organ-on-chip technology has introduced a new approach to reproducing organ-level physiology under experimentally controlled conditions. A landmark lung-on-chip model demonstrated that microengineered systems could recreate a functional alveolar-capillary interface while incorporating fluid flow and mechanically induced tissue deformation [3]. Subsequent advances have expanded the technology to multiple tissues and organs, with modern organ-on-chip platforms incorporating human-derived cells, three-dimensional tissue organization, extracellular matrices, vascular-like perfusion, biochemical gradients, and organ-specific mechanical forces [4]. Unlike conventional static cultures, these systems can reproduce dynamic microenvironmental cues that directly influence cellular phenotype, barrier integrity, and drug transport.

This capability is particularly important for nanocarrier evaluation because nanoparticle behaviour is governed not only by composition but also by particle size, morphology, surface charge, hydrophobicity, ligand functionalization, and interactions with surrounding biological molecules. These factors determine adhesion, mucus penetration, endocytosis, intracellular trafficking, transcytosis, retention, and clearance across different organ barriers [5]. Moreover, fluid velocity and shear stress within microfluidic devices can alter nanoparticle-cell interactions and therefore influence conclusions regarding transport and therapeutic efficacy. Barrier-on-chip systems enable these variables to be examined while simultaneously measuring functional endpoints such as molecular permeability, transepithelial or transendothelial electrical resistance, cellular uptake, and barrier disruption [6].

Organ-on-chip models therefore provide an opportunity to move nanocarrier assessment from relatively simplified permeability experiments toward mechanistically informative and quantitatively predictive testing. As illustrated in Figure 1, nanocarrier physicochemical characteristics interact with organ-specific barrier architecture and microenvironmental forces to determine transport mechanisms and measurable pharmacological outcomes. These experimental outputs can subsequently support prediction of tissue exposure, distribution, efficacy, and toxicity. Recent blood-brain-barrier-on-chip research, for example, demonstrates the value of combining human cellular components, physiological shear stress, three-dimensional extracellular matrices, and quantitative transport measurements for evaluating both

conventional therapeutics and complex nanocarriers [7]. Multi-organ platforms extend this concept further by linking absorption, distribution, metabolism, and elimination processes within interconnected human-relevant systems [8].

Accordingly, this review critically examines the use of organ-on-chip models for evaluating nanocarrier transport across major biological barriers. Particular attention is given to the architecture of these platforms, mechanisms and quantitative assessment of nanocarrier transport, barrier-specific applications, predictive performance, and translational relevance. The review further considers how organ-on-chip-derived data may be integrated with computational, pharmacokinetic, and artificial-intelligence-based models to strengthen the translation of nanocarrier drug-delivery systems from preclinical development to clinical application.

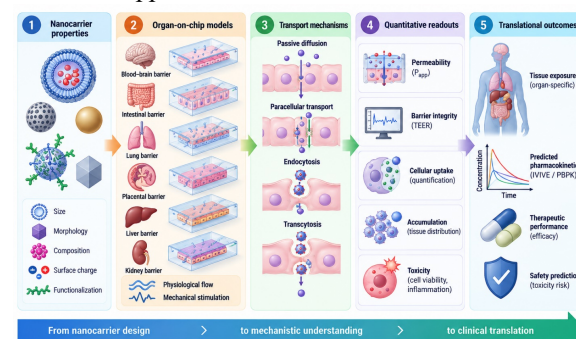


Figure 1. Conceptual framework for organ-on-chip-guided evaluation of nanocarrier transport across biological barriers. Nanocarrier physicochemical properties, including size, morphology, composition, surface charge, and functionalization, interact with organ-specific biological barriers recreated within microfluidic platforms under physiological flow and mechanical stimulation. Resulting transport processes—including diffusion, paracellular movement, endocytosis, and transcytosis—are quantified through permeability, barrier-integrity, cellular-uptake, accumulation, and toxicity measurements. These experimental outputs provide data for predicting tissue exposure and translational drug-delivery performance.

2. Organ-on-Chip Platforms for Nanocarrier Transport

Organ-on-chip platforms are microengineered culture systems designed to reproduce critical structural, cellular, biochemical, and mechanical characteristics of human tissues within controlled microfluidic environments. In contrast to conventional static culture models, these platforms permit continuous medium perfusion, generation of physiologically relevant shear stress, spatial organization of multiple cell types, and incorporation of extracellular matrix components. Such features are especially valuable for

nanocarrier evaluation because nanoparticle transport is highly sensitive to local fluid dynamics, cell-cell interactions, extracellular architecture, and the integrity of epithelial or endothelial interfaces [4,9]. Barrier-on-chip systems can therefore provide a more physiologically relevant environment for assessing permeability, cellular uptake, retention, toxicity, and translocation than conventional two-dimensional assays.

The basic architecture of a barrier-on-chip commonly consists of two or more microfluidic channels separated by a porous membrane, hydrogel matrix, or directly formed tissue interface. One channel generally represents the luminal or vascular compartment, while the opposing compartment reproduces the surrounding tissue environment. Endothelial and epithelial cells may be cultured on opposite surfaces of a membrane or arranged within extracellular matrices to recreate tissue-specific organization. Continuous perfusion exposes cells to mechanical forces that influence morphology, polarization, junctional organization, transporter expression, and overall barrier function [6,9]. These characteristics are particularly important when investigating nanocarriers because their contact with the cellular surface and subsequent internalization may change substantially between static and dynamic flow conditions.

Reliable assessment of barrier integrity is essential before nanocarrier transport data can be interpreted. Molecular permeability assays using fluorescent tracers provide a direct estimate of paracellular leakage, whereas transepithelial or transendothelial electrical resistance (TEER) offers a non-invasive measure of ionic resistance across the cellular barrier. Integration of TEER electrodes into microphysiological systems enables repeated or continuous monitoring without disrupting the cultured tissue [10]. Recent standardized platforms have further demonstrated that integrated TEER sensing can be combined with controlled perfusion and conventional multiwell formats, improving compatibility with higher-throughput permeability and toxicity studies [11]. Such measurements are important because an increase in detected nanocarrier passage may otherwise be incorrectly interpreted as efficient transport when it actually results from damage or loss of barrier integrity.

The material used to fabricate an organ-on-chip also influences experimental reliability. Polydimethylsiloxane (PDMS) remains widely used because it is transparent, flexible, gas permeable, and suitable for rapid microfabrication. However, its tendency to absorb or adsorb hydrophobic compounds can alter the effective concentration of test agents and complicate quantitative drug-transport measurements [12]. Surface modification, alternative polymers,

thermoplastics, and antifouling coatings are therefore increasingly being investigated to reduce nonspecific interactions. These considerations are especially relevant for lipid-based and polymeric nanocarriers, for which interactions with channel walls may influence apparent recovery and transport.

Cell selection is another major determinant of physiological relevance. Primary human cells, immortalized cell lines, induced pluripotent stem cell-derived cells, organoid-derived tissues, and multicellular co-cultures have all been incorporated into organ-on-chip platforms. Increasing cellular complexity can improve tissue-specific function, but it may also increase experimental variability and complicate standardization.[13] Accordingly, platform selection should balance physiological fidelity with reproducibility, scalability, and compatibility with quantitative analysis. The key characteristics that determine the suitability of organ-on-chip platforms for nanocarrier studies are summarized in Table 1.

Table 1. Key Characteristics of Organ-on-Chip Platforms Relevant to Nanocarrier Evaluation

Platform characteristic	Typical implementation	Relevance to nanocarrier evaluation	Major considerations
Microfluidic architecture	Parallel channels, membrane-separated chambers, hydrogel channels	Reproduces compartmentalized transport and tissue interfaces	Channel dimensions and geometry influence flow and transport
Physiological perfusion	Continuous or recirculating medium flow	Simulates vascular exposure and nanoparticle-barrier interactions	Flow rate and shear stress require physiological optimization
Cellular composition	Endothelial, epithelial, stromal and immune cells	Improves tissue-specific uptake and transport behaviour	Cell source affects reproducibility and phenotype
Extracellular matrix	Collagen, fibrin, Matrigel	Recreates tissue support and	Matrix composition may

	or synthetic hydrogels	three-dimensional transport environment	alter nanocarrier diffusion
Barrier-integrity assessment	TEER, permeability tracers, junctional-marker analysis	Distinguishes true nanocarrier transport from barrier disruption	Measurement methods require appropriate calibration
Integrated imaging/sensing	Fluorescence microscopy, biosensors, electrical sensing	Enables real-time monitoring of uptake, transport and toxicity	Device design must permit optical or electrical access
Device material	PDMS, glass, thermoplastics or coated polymers	Determines drug/nanocarrier recovery and assay reliability	Adsorption or absorption can influence measured concentration
Scalability	Single-chip to multiwell-compatible platforms	Supports comparative formulation screening	Greater throughput may reduce structural complexity

Collectively, organ-on-chip systems provide a controllable interface between nanomedicine and human-relevant barrier physiology. Their principal advantage lies not merely in reproducing tissue architecture but in allowing nanocarrier behaviour to be evaluated under defined mechanical and biological conditions while barrier function is simultaneously monitored. This combination establishes the foundation for mechanistic investigation of how nanocarriers cross biological interfaces, which is addressed in the following section.

3. Mechanisms and Quantitative Assessment of Nanocarrier Transport

Transport of nanocarriers across biological barriers is governed by a combination of carrier-specific physicochemical properties and the structural and functional characteristics of the barrier itself. Unlike small molecules that may cross cellular interfaces by

passive diffusion, nanocarriers frequently depend on energy-dependent processes such as endocytosis, intracellular trafficking, and transcytosis. Paracellular transport through intercellular junctions is generally restricted in highly organized barriers, whereas transcellular pathways permit nanocarriers to enter cells through vesicular mechanisms and subsequently reach the opposite side of the tissue interface.[5,14] Receptor-mediated transcytosis is particularly relevant for targeted nanocarriers because surface ligands can interact with specific membrane receptors and promote vesicular transport across otherwise restrictive barriers. Adsorptive-mediated transcytosis may also facilitate transport through electrostatic interactions between positively charged nanocarriers and negatively charged cellular membranes.[14]

The efficiency of these mechanisms is strongly influenced by nanocarrier size, morphology, surface charge, elasticity, hydrophobicity, and chemical composition. Particle size is a critical determinant of circulation, cellular internalization, tissue penetration, and clearance, although its biological influence cannot be interpreted independently of polydispersity, colloidal stability, and surface properties.[15] Similarly, surface charge affects interactions with cellular membranes and extracellular components, while particle shape may influence membrane adhesion, uptake kinetics, and movement through confined biological spaces. Emerging nanocarriers with transformable size, shape, or surface charge have been designed to adapt to different physiological environments, thereby improving their ability to overcome sequential biological barriers.[16] Protein adsorption following exposure to biological fluids further modifies the original nanocarrier surface and may alter receptor recognition, cellular uptake, biodistribution, and pharmacokinetic behaviour.[17]

Quantitative assessment is essential for distinguishing efficient nanocarrier transport from nonspecific leakage caused by compromised barrier integrity. Apparent permeability coefficients, transport or translocation efficiency, cellular uptake, intracellular accumulation, retention, and recovery across donor and receiver compartments are commonly used to characterize nanocarrier movement. Fluorescence microscopy and labelled nanocarriers can provide spatial information regarding cellular localization and translocation, whereas quantitative analytical methods can determine the amount of transported carrier or associated drug. These measurements should be interpreted together with barrier-integrity indicators rather than as isolated endpoints.[6]

Transepithelial or transendothelial electrical resistance and molecular permeability assays provide complementary information regarding barrier function.[6,10] A decline in electrical resistance or

increased passage of a paracellular tracer during nanocarrier exposure may indicate disruption of tight junctions rather than genuine carrier-mediated transport. Conversely, nanocarrier passage in the presence of preserved barrier resistance and low tracer permeability provides stronger evidence for controlled transcellular or transcytotic movement. Organ-on-chip systems are particularly advantageous in this context because transport, barrier integrity, flow-dependent interactions, and cellular responses can be evaluated simultaneously under controlled physiological conditions. Combining these quantitative endpoints with rigorous nanocarrier characterization is therefore essential for generating transport data that can subsequently be compared across biological barriers and translated into predictive drug-delivery models.

4. Nanocarrier Transport Across Major Biological Barriers

The transport behaviour of nanocarriers varies considerably among biological barriers because each tissue possesses a distinct cellular architecture, junctional organization, extracellular environment, vascular structure, and physiological function. Organ-on-chip systems provide an opportunity to recreate these barrier-specific conditions while permitting controlled evaluation of nanocarrier penetration, uptake, accumulation, and toxicity. Among these models, the blood-brain barrier (BBB) has received particular attention because its highly selective endothelial interface severely restricts entry of many therapeutic molecules into the central nervous system. BBB-on-chip platforms incorporate brain microvascular endothelial cells together with supporting pericytes, astrocytes, or neural cells under perfusion to reproduce major components of the neurovascular unit.[7] These platforms are increasingly used to investigate receptor-mediated transcytosis, adsorptive transport, nanoparticle uptake, and barrier permeability. Surface-engineered nanocarriers capable of interacting with endothelial receptors may improve brain delivery; however, enhanced cellular uptake does not necessarily ensure successful trans-barrier transport, making quantitative measurement of both internalization and transcytosis essential.[14]

The intestinal barrier represents another important interface because orally administered nanocarriers must encounter mucus, digestive conditions, epithelial cells, tight junctions, and intestinal transporters before reaching the systemic circulation. Microfluidic intestinal models can reproduce epithelial polarization, mucus production, villus-like structures, continuous flow, oxygen gradients, and interactions with endothelial, immune, and microbial components.[18] Such systems provide a more dynamic platform for determining whether nanoparticle size, surface

chemistry, mucoadhesion, or mucus penetration enhances intestinal absorption. For example, smaller particles may diffuse more efficiently through mucus, whereas surface modifications can alter both epithelial interactions and cellular uptake.[15] Nevertheless, increased uptake must be differentiated from intracellular retention because only nanocarriers capable of crossing the epithelial interface contribute directly to systemic delivery.

The pulmonary barrier is particularly relevant to inhaled nanomedicines because it combines a thin epithelial interface with an air-liquid environment, vascular perfusion, surfactant, and cyclic mechanical deformation. Lung-on-chip models can recreate breathing-associated stretch together with epithelial-endothelial interactions, allowing nanocarrier deposition, internalization, translocation, and inflammatory effects to be evaluated under physiologically relevant mechanical conditions.[19] Nanoparticle size, shape, surface charge, and formulation properties interact with shear stress and cyclic stretch to influence transport and therapeutic response. Consequently, pulmonary chip systems may provide information that cannot be obtained reliably from static cell monolayers, particularly when evaluating formulations intended for local lung delivery or systemic absorption through the alveolar interface.

The placental barrier presents a different translational challenge because drug delivery must be evaluated alongside potential fetal exposure. Placenta-on-chip models reproduce the maternal-fetal interface by combining trophoblast and endothelial layers under controlled flow. A recent human placenta-on-chip model generated from trophoblast stem cells demonstrated that nanoparticle exposure could alter trophoblast differentiation, hormone secretion, glucose transport, inflammatory signalling, and endothelial barrier integrity.[20] This illustrates that organ-on-chip platforms can evaluate not only particle transfer but also barrier-specific toxicity. Such models may therefore be particularly valuable for assessing nanomedicines intended for use during pregnancy, where both therapeutic efficacy and fetal safety must be considered.

Tumor-associated barriers differ substantially from healthy vascular interfaces because nanocarrier delivery is affected by abnormal vasculature, heterogeneous permeability, dense extracellular matrix, elevated interstitial pressure, and variable cellular composition. Tumor-on-chip systems reproduce several of these characteristics and permit direct visualization of nanoparticle extravasation, matrix penetration, cellular uptake, therapeutic response, and resistance under dynamic conditions.[21] These platforms are especially

valuable for examining the relative contributions of passive accumulation and active transport mechanisms, which remain important considerations in cancer nanomedicine. The physicochemical adaptability of nanocarriers, including changes in size or surface characteristics, may further improve penetration through sequential vascular and tumor-matrix barriers.[16]

Kidney-on-chip systems extend barrier modelling to glomerular filtration and tubular handling. Microfluidic models have been developed for the glomerulus, proximal tubule, distal tubule, collecting duct, and interconnected nephron-like systems.[22] These platforms may help determine whether nanocarriers undergo filtration, tubular uptake, renal accumulation, or nephrotoxic interactions. Likewise, skin-on-chip systems reproduce important aspects of epidermal and dermal organization and are being explored for transdermal delivery and toxicity assessment.[23] Their application to nanocarrier research may improve understanding of particle penetration through the stratum corneum and subsequent interaction with deeper cellular layers.

Despite substantial differences among these biological interfaces, several common determinants govern nanocarrier transport, including particle size, surface charge, morphology, ligand density, protein adsorption, flow conditions, and barrier integrity.[15-17] As summarized in Table 2, organ-on-chip models enable these parameters to be studied within barrier-specific physiological environments rather than as isolated formulation characteristics. This comparative approach is essential for determining whether observed nanocarrier transport reflects a broadly applicable delivery mechanism or a response unique to a particular tissue microenvironment.

Table 2. Comparative Evaluation of Nanocarrier Transport Across Major Biological Barrier-on-Chip Models

Biological barrier	Major physiological features reproduced	Nanocarrier-related transport process	Key assessment endpoints	Principal translational application	Major limitation
Blood-brain barrier	Brain endothelium, astrocytes/pericytes,	Endocytosis and receptor-	TEER, permeability, uptake	Prediction of brain-target	Difficult reproduction of com

	tight junctions, shear stress	/adsorptive-mediated transcytosis	endothelial transcytosis, accumulation	drug delivery	neurovascular complexity
Intestinal barrier	Polarized epithelium, mucus, villus architecture, flow, microbial/immune interactions	Mucus penetration, epithelial uptake and translocation	Permeability, TEE R, uptake, mucus interaction	Prediction of oral nanocarrier absorption	Variation in mucus, microbiota and cell composition
Pulmonary barrier	Air-liquid interface, alveolar epithelium, endothelium, cyclic stretch	Deposition, cellular uptake and alveolar translocation	Particle deposition, permeability, inflammatory response	Evaluation of inhaled nanomedicines	Difficulty reproducing complete respiratory mechanics
Placental barrier	Trophoblast-endothelial interface and maternal-fetal flow	Maternal-to-fetal nanoparticle transfer and cellular uptake	Barrier integrity, transport, hormone secretion, toxicity	Pregnancy-related drug and nanotoxicity assessment	Gestational-stage-specific physiology is difficult to reproduce
Tumor/vascular	Abnormal vasculature	Extravasation,	Accumulation,	Prediction of	High tumor

barrier	ture, extracellular matrix, perfusion and tumor cells	matrix penetration and tumor uptake	penetration depth, uptake, therapeutic efficacy	cancer nanomedicine performance	heterogeneity
Renal barrier	Glomerular filtration and tubular microenvironment	Filtration, tubular uptake and renal retention	Permeability, accumulation, toxicity	Renal targeting and nephrotoxicity prediction	Incomplete replication of whole-nephron physiology
Skin barrier	Epidermal and dermal organization	Surface penetration and transdermal transport	Penetration depth, permeability, cellular toxicity	Transdermal nanocarrier development	Full skin appendages and immune components are difficult to reproduce

5. Predictive Performance and Translational Relevance

The translational value of an organ-on-chip model ultimately depends on whether its experimental outputs can predict responses that occur in humans rather than merely reproduce tissue-like morphology in vitro. Conventional two-dimensional cultures provide reproducible and relatively inexpensive screening systems but lack physiological flow, multicellular interactions, three-dimensional organization, and mechanical stimulation. Animal models incorporate systemic physiology but can generate species-dependent responses that do not

accurately reflect human pharmacokinetics, toxicity, or therapeutic efficacy. Human microphysiological systems attempt to bridge this gap by reproducing organ-specific functions using human cells under controlled dynamic conditions.[24,25] For nanocarrier development, this distinction is important because nanoparticle uptake, transcytosis, tissue retention, and toxicity are highly dependent on biological microenvironment and cannot be predicted reliably from physicochemical characterization alone.

Evidence supporting the predictive potential of organ-on-chip technology has increased substantially. In a blinded performance assessment involving known hepatotoxic and non-hepatotoxic drugs, a human Liver-Chip achieved a sensitivity of 87% and specificity of 100% for prediction of drug-induced liver injury.[24] Although this study evaluated small-molecule toxicity rather than nanocarrier transport, it provides an important proof of principle that appropriately validated microphysiological systems can reproduce clinically relevant responses that may be missed by conventional preclinical approaches. More broadly, human microphysiological systems have demonstrated improved reproduction of organotypic function and disease-related responses compared with traditional two-dimensional models.[25] These findings support the development of similarly rigorous validation strategies for nanocarrier-specific barrier models.

For drug-delivery applications, predictive performance should be assessed through quantitative comparison of organ-on-chip outputs with established in-vivo or human data. Relevant parameters include apparent permeability, absorption fraction, tissue accumulation, clearance, cellular uptake, translocation efficiency, toxicity, and concentration-time profiles. Pharmacokinetic translation is particularly important because transport measured within an isolated chip does not automatically represent whole-body exposure. Organ-on-chip models intended for pharmacokinetic prediction therefore require physiologically relevant flow rates, tissue scaling, drug concentrations, sampling strategies, and validated reference compounds.[26] Multi-organ systems may further improve predictive capacity by linking intestinal absorption with hepatic metabolism, renal elimination, or target-tissue exposure.

Clinical concordance also requires careful differentiation between mechanistic plausibility and demonstrated predictive validity. A nanocarrier may exhibit enhanced permeability in a barrier-on-chip model, but this observation becomes translationally meaningful only when the measured response correlates with an appropriate in-vivo or clinical endpoint. Recent analyses therefore emphasize fit-for-purpose validation, standardized sampling,

quantitative biosensing, and benchmarking against clinical pharmacokinetic, toxicological, or biomarker datasets.[27] For barrier-focused nanomedicine, this could involve comparing chip-derived permeability with known tissue exposure, evaluating whether receptor-targeted carriers reproduce expected transport trends, and determining whether nanoparticle-induced barrier disruption observed on-chip corresponds with established biological responses.

Regulatory interest in microphysiological systems further strengthens their translational potential. In September 2024, the US Food and Drug Administration accepted the first organ-on-chip letter of intent into its Innovative Science and Technology Approaches for New Drugs program for a human Liver-Chip intended to assess drug-induced liver injury.[28] This development does not imply universal regulatory acceptance of organ-on-chip data, but it demonstrates movement toward formal qualification of microphysiological systems for defined contexts of use. Similar acceptance for nanocarrier transport models will require clear performance standards, reproducibility across laboratories, appropriate positive and negative controls, and direct comparison with established reference datasets.

The relative predictive strengths and remaining limitations of organ-on-chip approaches are summarized in Table 3. At present, these platforms should be viewed primarily as complementary tools rather than complete replacements for every conventional preclinical model. Their greatest translational value lies in generating human-relevant mechanistic and quantitative data that can be integrated with pharmacokinetic modelling, animal data where necessary, and clinical evidence. Establishing such cross-model correlations will be essential before barrier-on-chip platforms can routinely guide nanocarrier selection, dose optimization, and clinical translation.[26,27]

Table 3. Predictive and Translational Performance of Organ-on-Chip Models Relevant to Drug and Nanocarrier Development

Predictive domain	Organ-on-chip capability	Comparative/validation approach	Translational value	Current limitation
Barrier permeability	Quantifies transport under controlled	2D/Transwell permeability and in-vivo exposure	Improved assessment of tissue	Limited standardized cross-platform

	flow and intact tissue interfaces		penetration	thresholds
Cellular uptake and transcytosis	Enables visualization and quantitative analysis of carrier internalization and transport	Static cell models and tissue-distribution studies	Mechanistic evaluation of targeted nanocarriers	Uptake does not always predict systemic delivery
Toxicity prediction	Reproduces organ-specific responses using human cells	Animal toxicology and clinical toxicity datasets	Potential earlier identification of human-specific toxicity	Validation remains organ- and context-specific
Pharmacokinetic prediction	Generates absorption, metabolism, transport, and clearance parameters	Human PK and conventional ADME models	Supports IVIVE and PBPK model development	Physiological scaling remains challenging
Disease-specific response	Incorporates patient-derived	Clinical biomarkers and therapeutic response	Potential personalized treatment	Cell variability may reduce

	d or diseases-specific cells		ent prediction	reproducibility
Multi-organ disposition	Links absorption, metabolism, distribution, and elimination compartments	Whole-body animal or human PK profiles	More integrated prediction of systemic exposure	Technical complexity and throughput constraints
Regulatory translation	Provides human-relevant quantitative evidence for defined contexts of use	Qualification against benchmark compounds and clinical datasets	Potential use as a new approach methodology	Requires rigorous qualification and inter-laboratory validation

6. Integration with Computational and Pharmacokinetic Models

Although organ-on-chip systems provide physiologically relevant measurements of nanocarrier transport, isolated experimental observations cannot fully describe whole-body absorption, distribution, metabolism, and elimination. Integration of chip-derived data with computational pharmacokinetic approaches can therefore extend local barrier measurements into predictions of systemic exposure and tissue-specific delivery. Parameters such as permeability coefficients, cellular uptake, transcytosis rates, tissue retention, metabolism, and clearance obtained from microphysiological systems can serve as experimental inputs for in-vitro-in-vivo extrapolation (IVIVE) and physiologically based pharmacokinetic (PBPK) models.[26,29]

PBPK modelling is particularly relevant to nanomedicine because nanoparticles exhibit disposition mechanisms that differ substantially from

those of conventional small molecules. Particle size, surface chemistry, protein-corona formation, phagocytic uptake, tissue permeability, carrier degradation, and drug release can collectively determine biodistribution and clearance.[29] Mechanistic incorporation of these parameters enables simulation of concentration-time profiles across individual organs and may assist in identifying formulation characteristics that improve target-tissue exposure. For restrictive barriers such as the blood-brain barrier, PBPK approaches may also help translate experimentally measured permeability into predictions of brain exposure and evaluate whether surface modification is likely to improve nanocarrier transport.[29]

Artificial intelligence (AI) and machine-learning approaches provide an additional layer of analysis by processing high-dimensional imaging, sensor, molecular, and transport data generated by organ-on-chip platforms. AI-based approaches may support automated image analysis, phenotype classification, prediction of drug responses, optimization of experimental conditions, and identification of complex relationships between nanocarrier characteristics and biological outcomes.[30] More recently, integration of AI with organ-on-chip technology has been proposed as a bidirectional framework in which human-relevant experimental data improve computational models while computational predictions guide subsequent chip experiments.[31]

As illustrated in Figure 2, a translational workflow can therefore link nanocarrier characterization and organ-on-chip testing with quantitative transport measurements, IVIVE/PBPK modelling, and AI-assisted prediction. Such integration may ultimately permit estimation of human tissue exposure, therapeutic response, and toxicity before clinical testing. However, its reliability will depend on standardized experimental datasets, physiologically meaningful scaling, transparent computational assumptions, and validation against independent human pharmacokinetic observations.[26,29-31].

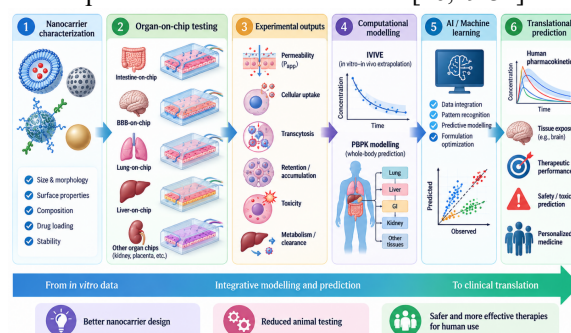


Figure 2. Integration of organ-on-chip-derived nanocarrier transport data with computational and pharmacokinetic models for translational

drug-delivery prediction. Physicochemical characterization of nanocarriers is followed by testing in organ-specific microphysiological systems to generate quantitative permeability, uptake, transcytosis, retention, toxicity, and clearance data. These experimental parameters can be incorporated into IVIVE and PBPK models and further analysed using artificial intelligence and machine-learning approaches to predict human pharmacokinetics, tissue exposure, therapeutic performance, and potential toxicity.

7. Challenges and Future Perspectives

Despite rapid progress in organ-on-chip technology, several technical and translational barriers continue to limit its routine application in nanocarrier development. One of the most important challenges is the absence of universally accepted standards for device design, cell sourcing, flow conditions, functional readouts, and validation criteria. Differences in channel geometry, membrane materials, extracellular matrices, and experimental protocols can produce substantial variability between laboratories and complicate direct comparison of nanocarrier transport data.[32] For meaningful translation, organ-on-chip models therefore require standardized performance parameters and benchmarking against clinically relevant reference data.

Reproducibility, scalability, and ease of use also remain important obstacles to wider industrial adoption. Recent stakeholder analyses have emphasized that organ-on-chip systems must provide reliable results across operators and laboratories while remaining compatible with routine pharmaceutical workflows.[33] For nanocarriers, additional challenges arise from nonspecific adsorption to device materials, variability in nanoparticle recovery, differences in protein-corona formation, and difficulties in reproducing clinically relevant concentrations and exposure times. These factors may alter apparent permeability or uptake and should be carefully controlled during model development.

Regulatory translation will similarly require clearly defined contexts of use, validated reference compounds or formulations, transparent data reporting, and independent assessment of model performance.[34] Current evidence indicates that regulatory readiness varies substantially among organ-specific systems, with some models having stronger validation than others.[35] Barrier-on-chip models used for nanomedicine will therefore need direct comparison with human pharmacokinetic, tissue-distribution, and toxicity data before they can support high-confidence regulatory decisions.

Future development is expected to move toward patient-derived and induced pluripotent stem cell

models, automated high-throughput platforms, integrated real-time biosensors, multi-organ systems, and AI-assisted data interpretation. As illustrated in Figure 3, the evolution from conventional organ-on-chip platforms toward standardized, interconnected, sensor-integrated, and computationally supported systems could enable increasingly personalized and clinically predictive evaluation of nanocarriers. Ultimately, successful translation will depend on combining biological complexity with reproducibility, quantitative validation, scalable manufacturing, and regulatory acceptance.[32-35].

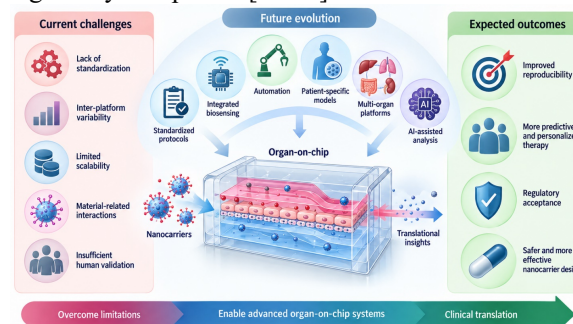


Figure 3. Current challenges and future evolution of organ-on-chip-guided nanocarrier development.

Current limitations—including lack of standardization, inter-platform variability, limited scalability, material-related interactions, and insufficient human validation—must be addressed through standardized protocols, quality-controlled manufacturing, integrated biosensing, automation, patient-specific cell models, multi-organ platforms, and AI-assisted analysis. These advances are expected to improve reproducibility and facilitate regulatory and clinical translation of nanocarrier-based drug-delivery systems.

8. Conclusion

Organ-on-chip technology offers a promising human-relevant approach for evaluating nanocarrier transport across complex biological barriers by combining controlled microfluidic environments with physiologically relevant cellular organization, flow, and functional barrier assessment. These platforms can provide mechanistic and quantitative information on permeability, cellular uptake, transcytosis, tissue accumulation, and toxicity that is difficult to obtain from conventional static models. Their integration with IVIVE, PBPK modelling, and AI-assisted analysis may further improve prediction of human pharmacokinetics and translational drug-delivery performance. However, differences in device architecture, cell sources, materials, experimental protocols, and validation strategies continue to limit inter-platform comparability and regulatory confidence. Future progress should therefore prioritize standardized workflows, clinically relevant

benchmarking, scalable platforms, and integration of patient-specific and multi-organ models. With continued validation, organ-on-chip systems could become valuable complementary tools for selecting, optimizing, and translating nanocarrier formulations toward safer and more effective human drug delivery.

Acknowledgements

The authors acknowledge the contributions of researchers whose studies have advanced the understanding of organ-on-chip technologies, nanocarrier transport, biological barrier modelling, and translational drug-delivery systems.

Funding

The authors received no specific funding for the preparation of this review article.

Conflict of Interest

The authors declare that there are no conflicts of interest associated with the preparation or publication of this manuscript.

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