Kratek pregled platform za ADME testiranje

A narrative review of ADME testing platforms

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Izvleček

Namen: *V zadnjem času je bil dosežen pomemben napredek pri razvoju ADME (absorpcija, distribucija, metabolizem, ekskrecija) modelov, vendar izziv ostaja vzpostaviti platforme, ki bi zmanjšale testiranje na živalih in stroške raziskav. Naraščajoča pomembnost farmakokinetičnih interakcij poudarja potrebo po zanesljivih in ponovljivih ADME modelih, ki so vse bolj ključni za razvoj zdravil in zagotavljanje varnosti z željo po preprečevanju resnih kliničnih zapletov in hospitalizacije.*

Metode: *Pregledna študija obravnava večorganske funkcijsko zasnovane ADME platforme in ocenjuje nedaven razvoj mikro-fizioloških sistemov (MPS), ki poudarek dajejo funkcionalni natančnosti. Osredotoča se na MPS modele, razvite za izboljšanje*

Abstract

Background: *Significant progress has been made in absorption, distribution, metabolism, excretion (ADME) models, but the creation of platforms that reduce animal testing and research costs is still challenging. The increasing complexity of pharmacokinetic interactions underscores the need for reliable, reproducible ADME models, which are essential for drug development and safety to prevent serious clinical complications and hospitalizations.*

Aims: *This narrative review aimed to discuss multi-organ, function-based ADME platforms and evaluate recent developments in microphysiological systems (MPS) emphasizing functional accuracy.*

Methods: *We evaluated MPS models developed to improve the relevance of in vitro drug interaction studies by*

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relevantnosti in vitro študij interakcij zdravil s poudarkom na ključnih funkcijah tkiv v primerjavi z natančno anatomsko reprodukcijo.

Rezultati: *Medtem ko so MPS modeli napredovali pri strukturnem posnemanju, pogosto primanjkuje funkcionalna natančnost, ki je ključna za natančno testiranje zdravil. Modeli, ki prednost dajejo funkcionalnosti pred kompleksnimi strukturnimi podrobnostmi, obetajo rezultate, ki so bolj relevantni za človeka in bi lahko ponudili alternativo testiranju na živalih.*

Zaključki: *Da bi v celoti izkoristili potencial MPS v ADME študijah, je potreben premik fokusa od anatomske kompleksnosti k posnemanju ključnih funkcij tkiv. S tem, ko naslovimo trenutne omejitve v biomedicinskem inženirstvu, bomo podprli etične, znanstvene in regulativne cilje predkliničnih raziskav. Osredotočanje na funkcionalno natančnost omogoča, da MPS platforme premostijo vrzel med tradicionalnimi modeli in človeku relevantnimi sistemi, kar bo povečalo translacijsko vrednost ADME študij in prispevalo k učinkovitemu in etičnemu razvoju zdravil.*

emphasizing critical tissue function over detailed anatomical mimicry. We also highlighted the strengths and limitations of these platforms in replicating the full complexity and functionality of native tissues.

Results: *Despite making progress in structural replication, MPS models often lack the functional fidelity required for accurate drug testing. Models that emphasize functionality rather than complex structural details show promise in producing results relevant to humans, thus providing an alternative to animal testing.*

Conclusions: *A shift in focus from anatomical complexity to mimicking key tissue functions is required to fully realize the potential of MPS in ADME studies. Addressing the current limitations of biomedical engineering in this way may support the ethical, scientific, and regulatory goals of preclinical research. MPS can bridge the gap between traditional models and human-relevant systems by emphasizing functional accuracy, thus increasing the translational value of ADME studies and contributing to effective, ethical drug discovery.*

INTRODUCTION

Advancements in the development of microphysiological systems (MPS), traditionally often referred to as organ-on-a-chip devices, have revolutionized the field of absorption, distribution, metabolism, and excretion (ADME) research over the past decade, creating promising alternatives to traditional drug discovery and development models (1, 2). Historically, animal models have served as the primary testing ground for ADME studies despite inherent limitations such as ethical concerns, high costs, and interspecies differences that frequently hinder the translatability of results to human outcomes. Considering an aging global population, the incidence of chronic conditions requiring multi-drug regimens has escalated, amplifying the potential for pharmacokinetic (PK) drug interactions and underscoring the need for predictive, human-relevant preclinical testing (Fig. 1). MPS models are designed to emulate human tissue environments at the microscale, and thus meet the aforementioned demands by providing models closely mirroring human-specific physiological responses, thereby enabling personalized treatment approaches (3). MPS not only help reduce animal use but also provide more accurate, reproducible, and ethically sound means of testing, thus aligning with the growing global emphasis on the 3Rs principle (Replacement, Reduction, and Refinement) in scientific research (4).

Despite these advances, many current MPS models face challenges in replicating the full complexity and functionality of native tissues (5). A primary issue is a trade-off between anatomical complexity and functional mimicry, where models often lean toward the former at the expense of adequately emulating tissue-specific functions, which is essential for accurate ADME studies (6). For instance, integrating vascular networks or stromal components in MPS can improve structural mimicry but does not necessarily translate into functional equivalence, particularly concerning cellular interactions and biochemical responses.

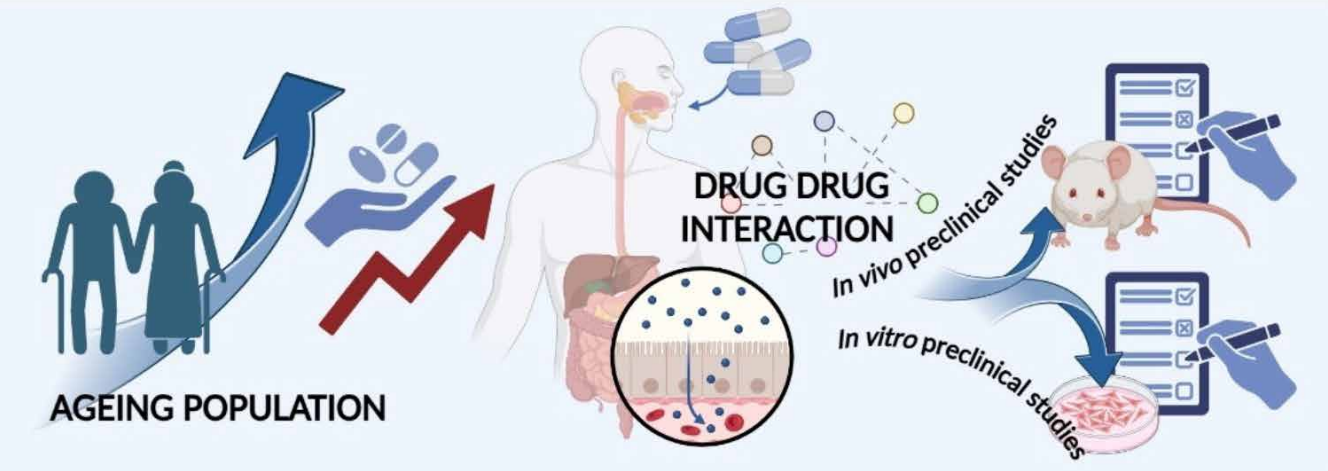

Figure 1. *Illustration of aging and increasing complexity of drug–drug interactions, with the transition from in vivo to in vitro preclinical studies. (Created with BioRender.com)*

Additionally, advancements in biomaterials and bioprinting technologies have improved the structural fidelity of these systems; however, a comprehensive understanding of biological processes within the microscale environments remains limited, impeding the creation of functionally robust MPS (7-9).

Biomedical engineering tools, including three-dimensional cell cultures, imaging techniques, and other analytical methods, together with advanced fabrication strategies for microfluidic devices and tissue scaffolds, such as additive manufacturing and electrospinning (10), have contributed significantly to MPS development. However, individually, these tools have inherent constraints (10, 11), which underscore the need for innovation in both design and material selection to achieve the high degree of functional mimicry required for ADME studies. We should also consider that MPS need not replicate the entire tissue architecture but rather focus on the essential functionalities critical to ADME processes, such as enzyme activity, cell membrane transport, and intercellular communication (12, 13).

With the continuous evolution of MPS technology, we should refine the approach to prioritize functional relevance over structural complexity. We can create models that more accurately simulate human drug responses by targeting specific functionalities, such as hepatic enzyme expression and renal filtration capacity, thereby enhancing their predictive power for nonclinical research applications. Such function-oriented MPS can facilitate the translation of ADME models to preclinical testing, eventually supporting the replacement of animal testing. Moreover, the refinement of MPS holds potential beyond ADME, extending into personalized medicine applications where patient-specific responses can be evaluated in vitro (14). Therefore, advancing MPS to meet these functional criteria will bring us closer to replicating human physiological responses and foster a more ethical, cost-effective, and human-relevant paradigm in drug development.

Current MPS models have laid a strong foundation, but transitioning from research prototypes to industry-standard tools requires a strategic shift toward functional fidelity (15). MPS can prioritize tissue-specific functions and address the technological limitations of existing biomedical tools, thus achieving the specificity and accuracy necessary to revolutionize ADME studies and, ultimately, transform nonclinical research methodologies.

RECENT ADME MODELS

Substantial progress has been made in MPS development tailored for ADME applications in recent years. Multiple reviews have documented

these advancements, thereby underscoring the diversity of MPS platforms designed to address tissue-specific ADME functions (16-20). Despite the strides made, the absence of a universal standard or global consensus regarding model characteristics has led researchers to pursue varied approaches. This variation reflects the need to prioritize structural complexity, functional mimicry, or scalability. The lack of a harmonized framework leads to difficulties in determining the specific features essential for accurate ADME modeling, consequently contributing to inconsistencies in replicability and predictive reliability across different systems (21).

MPS platforms for ADME have proven effective in replicating some individual tissue functions relevant to drug absorption (A) (22), distribution (D) (23), metabolism (M) (24) (Fig. 2), and excretion (E) (25). These platforms facilitate detailed studies on tissue-specific processes, offering insights into, for instance, how a compound may be absorbed through the intestine, distributed via the bloodstream, metabolized in the liver, or excreted by the kidneys. However, as pharmacological and toxicological research moves toward a more holistic understanding of drug effects, limitations of single-organ models have become apparent (26). Drug actions and interactions often depend on complex inter-organ communication and dynamic feedback loops, which is difficult for single-tissue systems to replicate fully. These inter-organ interactions are especially relevant for studies on aging populations, as organ function changes over time, which influences disease susceptibility and drug toxicity profiles (27).

Some models have attempted to bridge this gap by combining data from isolated ADME systems; however, they still lack the intricacy of in vivo feedback mechanisms critical for accurate PK assessment (28-30). PK processes are inherently dynamic and rely on real-time interactions between multiple organs. For example, a drug is absorbed, transported via the bloodstream, potentially metabolized by the liver before reaching its target site, and eventually excreted. Each stage of this journey influences the next, creating a cascade of interdependent events. Single-organ models cannot replicate these sequential processes, which limits their ability to predict systemic drug behavior accurately. Furthermore, without a cohesive, multi-organ setup, these models struggle to accurately assess drug–drug interactions—a critical aspect of drug development, especially when evaluating the safety and efficacy of combination therapies (31-33).

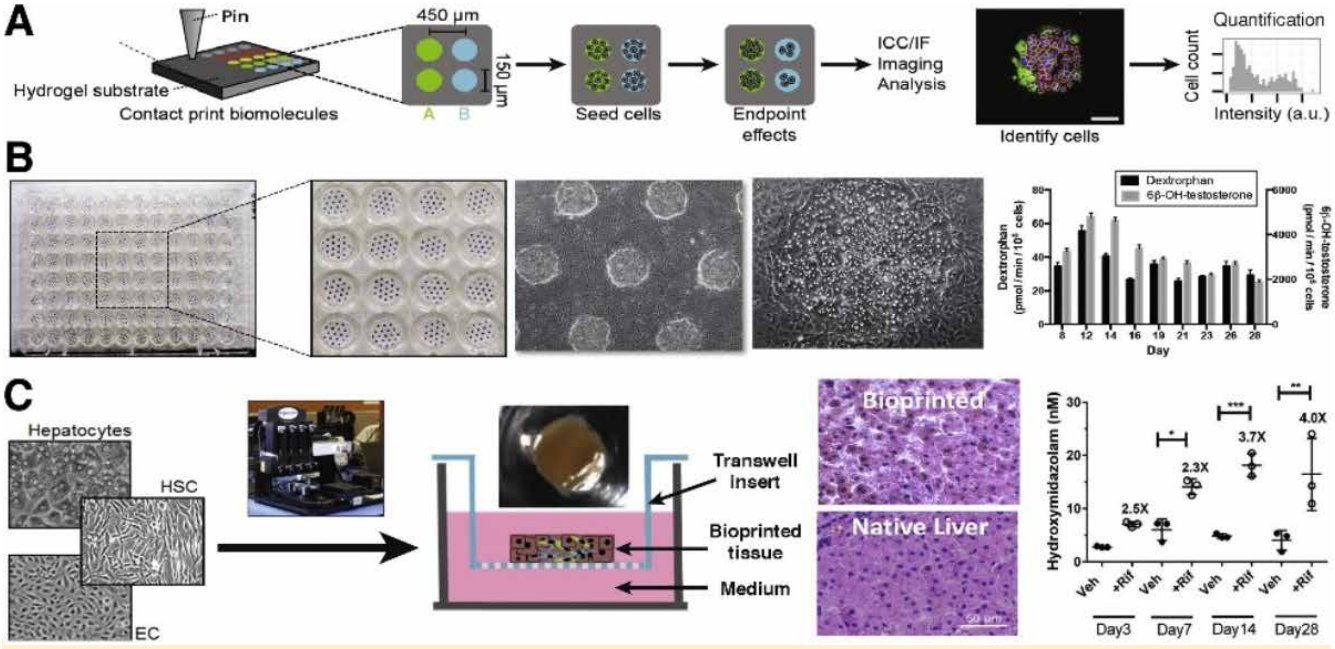

Figure 2. *Micropatterned/printed liver culture platforms (24).*

Nevertheless, the complete integration of all necessary components to fully replicate the drug-processing capabilities of the human body remains a significant technical challenge.

In response, emerging research now focuses on developing integrated MPS that couple multiple organ systems within a single ADME model (34). This approach seeks to emulate the full drug journey, from administration to excretion, with high functional accuracy. The most promising multi-organ systems incorporate liver, kidney, and intestinal modules, which are interconnected in ways that facilitate direct communication and simulate physiological conditions more closely (14). These platforms, often referred to as "body-on-a-chip" models, aim to create a dynamic environment where drugs circulate through various organ compartments, offering a more comprehensive view of PK and pharmacodynamics (PD) (35, 36).

Nevertheless, the complete integration of all necessary components to fully replicate the drug-processing capabilities of the human body remains a significant technical challenge.

A representative ADME model for comprehensive drug testing ideally features interconnected MPS platforms that accurately simulate the complete PK process, accounting for critical variables such as blood flow, tissue-specific compartments, and inter-organ feedback (Fig. 3). Additionally, these models must be scalable and reproducible to support high-throughput screening applications, which are essential for early-phase drug discovery. A function-focused approach, where models are optimized for key ADME functions rather than anatomical detail, can offer a practical balance. It can reduce the financial and time investments required to develop complex, anatomically accurate systems while still providing robust data on drug behavior.

The field of ADME MPS is moving toward integrated, multi-organ models capable of emulating the sequential stages of drug processing within the human body. Despite significant progress made, continued innovation and standardization are essential to realizing models that balance cost, complexity, and reliability, ultimately supporting more predictive, human-relevant preclinical testing frameworks (37-41).

IMPORTANCE OF ADME MODELS FOR CURRENT HEALTH CHALLENGES

Data from animal and simple in vitro models often do not translate effectively to human clinical trials, with failure rates in Phase II/III trials reaching up to 80% (42, 43). These limitations are attributed to genetic

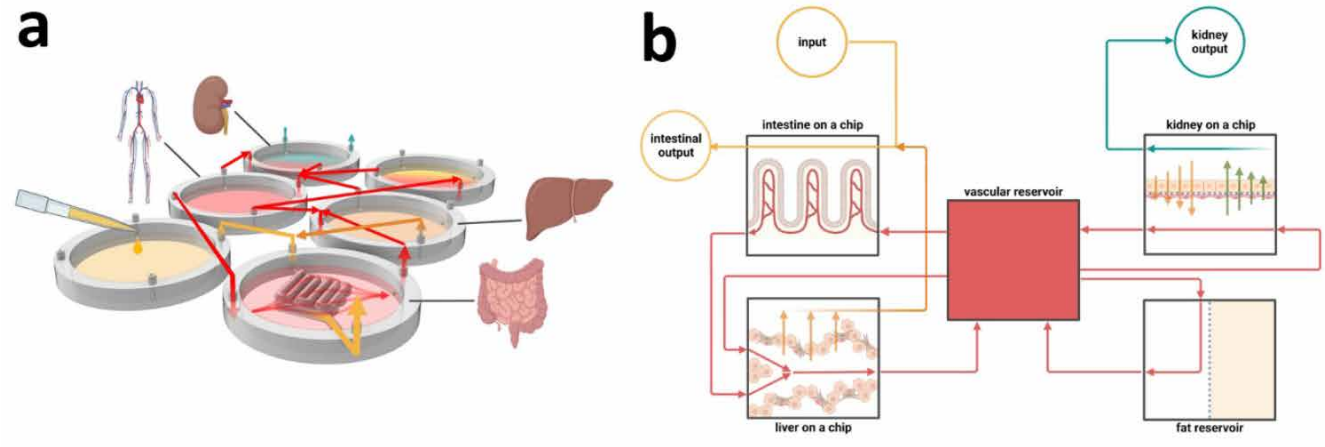

Figure 3. *(a) Proposed MPS platform with modular inserts in multi-well plates, connected through tubing and perfused via a peristaltic pump. (b) Schematic representation of the "journey" of an orally administered drug through the ADME model, depicting absorption in the intestines, distribution into fat tissue, liver metabolism, and kidney excretion. (Created with BioRender.com)*

Figure 4. *Need for improved ADME platforms, driven by aging populations, increased chronic drug use, and demand for platforms capable of evaluating drug interactions in complex PK scenarios. (Created with BioRender.com)*

and physiological differences, alongside the limitations of oversimplified in vitro models (44, 45). They result in models that cannot fully mimic the intricacy of human biological responses, leading to discrepancies that ultimately hinder the successful translation of findings into safe and effective treatments for humans. Furthermore, the aging of the global population and the increasing prevalence of chronic health conditions have led to a rising demand for robust and reliable testing platforms to facilitate timely drug development (46).

Figure 4 illustrates the key drivers for developing improved ADME platforms. The motivations for these advancements extend beyond basic research; affordable, scalable, and effective models that can predict human drug responses with greater fidelity need to be developed (47). Although complete structural and functional replication of human tissue is an ideal goal, it remains an impractical and resource-intensive endeavor. Instead, simplified models prioritizing key functional attributes offer a more attainable solution, improving reproducibility and accessibility while providing meaningful insights into human biology. Such models are more likely to be widely adopted by researchers to overcome the limitations in budget, infrastructure, and expertise. Therefore, focusing on functional aspects rather than the complexity of native tissue structures is a more feasible strategy for advancing preclinical research.

Several innovative approaches for developing in vitro ADME models have emerged in response to the aforementioned demands. Some of these strategies aim to mimic the intricate anatomical characteristics of native tissues, seeking to replicate specific structures and cellular arrangements to improve the physiological relevance of the models (48). Other approaches emphasize the increased functionality offered by MPS, which incorporates multiple organ-like structures and complex fluid dynamics to simulate inter-organ communication, nutrient flow, and waste removal, thus closely mirroring the interconnected environment within the human body. Table 1 provides

Table 1: *A comparison of some exemplary ADME models with their advantages and limitations*

Target property	References	Advantage	Limitations
Mimicking native tissue complexity and inter-organ communication	- Khalil et al. (2) - Ingber (14) - Picollet-D'hahan et al. (49)	Data generation that could reveal novel therapeutic compounds Comprehensive replication of tissue anatomy, physiology, and function	Limited reproducibility and accessibility Dependence on specialized knowledge, skills, and costly infrastructure Lack of standardized protocols and testing kits
Increasing MPS complexity	- Fowler et al. (21) - Ramadan et al. (3) - Ishida (35)	Representation of multi-organ communication, nutrient, and waste management Inline/online screening capabilities Integrated sensing for real-time data	High costs Research field monopolization risk by a few prominent groups

an overview of recent studies illustrating the two categories of ADME models (mimicking anatomical characteristics of native tissues and increasing functionality of MPS), highlighting their individual advantages and limitations.

CONCLUSIONS

MPS have shown significant promise for advancing ADME research; however, balancing anatomical complexity with functional fidelity is still challenging. Current MPS models often prioritize structural replication, yet functional accuracy is essential for meaningful drug testing and predictive outcomes. Future research should prioritize the mimicry of key tissue functions over structural intricacies to fully realize the potential of MPS in drug development and as an alternative to animal testing. MPS can bridge the gap between traditional models and human-relevant in vitro systems by addressing limitations in biomedical engineering tools and focusing on functionality. Ultimately, this shift may enhance the translational value of MPS in ADME studies, subsequently advancing the ethical, scientific, and regulatory landscape of preclinical research.

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