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Organoids and Organ-on-A-Chip Technologies as Advanced Platforms for Drug Testing and Safety Evaluation

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Abstract: Preclinical experimental models play a critical role in evaluating drug safety, efficacy, and pharmacokinetic behaviour prior to clinical trials. Conventional two-dimensional (2D) cell cultures and animal models have long been used in drug discovery; however, their limited ability to accurately reflect human physiology has contributed to high failure rates during clinical development. Species-specific differences in animal models and the oversimplified nature of 2D cultures often result in poor prediction of human toxicity and therapeutic response. To address these limitations, advanced human-relevant platforms such as three-dimensional (3D) organoids and organ-on-a-chip technologies have gained increasing attention. Organoids, derived from stem cells, mimic key aspects of human tissue architecture and function, enabling improved assessment of drug responses and organ-specific toxicity. Organ-on-a-chip systems further enhance physiological relevance by incorporating micro fluidic environments that simulate dynamic mechanical and biochemical conditions. Together, these emerging technologies offer promising alternatives to traditional preclinical models by improving translational accuracy, reducing late-stage drug attrition, and supporting safer and more efficient drug development.
Keywords: Drug discovery, Preclinical models, Organoids, Organ-on-a-chip, Drug toxicity.

1. Introduction

Reliable preclinical models are essential for identifying safe and effective drug candidates before they enter clinical trials. For decades, drug discovery has depended largely on two-dimensional (2D) cell cultures and animal models to evaluate pharmacological activity and toxicity. While 2D cell systems are easy to maintain and suitable for large-scale screening, they lack the structural complexity, cellular interactions, and physiological environment found in human tissues, which limits their predictive value [1]. Animal studies offer a more integrated biological context; however, differences between animal and human biology—particularly in metabolism and disease pathways—often result in poor translation of preclinical findings to clinical outcomes [2].

The frequent failure of drug candidates during late-stage development, often due to unforeseen toxicity or insufficient efficacy, has driven the search for more

human-relevant experimental platforms [3]. Advances in stem cell research and bioengineering have led to the development of three-dimensional (3D) organoid models that can self-organize into tissue-like structures resembling human organs. These systems capture key aspects of tissue organization and function, enabling more accurate assessment of drug responses and organ-specific toxicities [4]. In addition, organ-on-a-chip technologies combine living human cells with micro fluidic devices to recreate dynamic physiological conditions such as mechanical stress and fluid flow, further improving biological relevance [5].

Together, organoids and organ-on-a-chip platforms address many limitations of traditional models and represent powerful tools for enhancing drug safety evaluation and translational success.

2. Limitations of conventional drug testing methods

Two-dimensional (2D) cell culture systems have long served as a cornerstone of biomedical research and early-stage drug discovery. In these models, cells are cultured as a single layer on flat surfaces such as plastic or glass. Their straightforward handling, low cost, reproducibility, and suitability for high-throughput formats have made 2D cultures the preferred in vitro platform for decades, particularly during the initial phases of compound evaluation. As a result, they are routinely employed for early toxicity screening, mechanistic investigations, and basic pharmacological studies [1].

Within drug discovery workflows, 2D cell culture models are commonly applied to evaluate:

- Cytotoxic and ant proliferative effects of small molecules and biologics
- Drug–target interactions and underlying mechanisms of action
- Early indicators of absorption, distribution, metabolism, and excretion (ADME) behaviour [2].

Although these systems offer practical advantages, many drug candidates that demonstrate promising activity in 2D assays ultimately fail during animal studies or clinical trials. This high attrition rate has raised concerns regarding the translational reliability and predictive accuracy of conventional 2D culture platforms [6].

2.1 Limitations of 2D Cell Culture Models in Drug Testing

1. Inability to Reproduce the Physiological Microenvironment

A major drawback of 2D cell cultures is their limited ability to reflect the native cellular microenvironment. In vivo, cells exist within a complex three-dimensional architecture, where they are continuously influenced by mechanical forces, biochemical gradients, and intercellular communication. In contrast, cells grown on rigid, flat substrates lack exposure to these spatial and biochemical cues, resulting in cellular behaviours that differ substantially from those observed in living tissues [7].

2. Altered Drug Responsiveness and Gene Expression Profiles

Cells maintained in 2D monolayer are often more sensitive to therapeutic agents than their counterparts in structured tissue environments. This heightened sensitivity arises because drugs have unrestricted access to cells, without diffusion barriers or concentration gradients. Consequently, drug efficacy may be overestimated, increasing the risk of false-positive outcomes during early screening stages [8].

3. Limited Cell–Cell and Cell–Extracellular Matrix Interactions

In physiological tissues, cells constantly interact with neighboring cells and the extracellular matrix (ECM), interactions that are essential for regulating signaling cascades, differentiation, survival, and responses to external stimuli. These interactions are largely absent or simplified in 2D systems, significantly reducing their biological relevance [9].

4. Weak Predictive Capability for ADME-Toxicity

Because 2D cultures fail to recapitulate tissue complexity, they often provide limited insight into ADME-Tox characteristics. Key processes such as drug metabolism, transporter activity, and organ-specific toxicity are not accurately reflected, reducing the utility of 2D models for predicting clinical safety and efficacy outcomes [6].

5. Absence of Tissue-Like Gradients and Structural Organization

Native tissues exhibit gradients of oxygen, nutrients, and signaling molecules that critically influence cellular behavior, stress responses, and drug resistance mechanisms. Such gradients are missing in the homogeneous environment of 2D cultures. Moreover, essential features such as vascular networks, immune cell infiltration, and metabolic compartmentalization are absent, further limiting the ability of these models to accurately represent drug distribution, efficacy, and toxicity [9].

2.2 Animal models

Animal models have long been a cornerstone of preclinical drug development, providing a whole-organism context to study pharmacokinetics (PK), pharmacodynamics (PD), safety, and therapeutic efficacy prior to initiation of human clinical trials. Over the years, these models have significantly advanced our understanding of normal physiology, disease pathogenesis, and therapeutic mechanisms, and they remain a regulatory requirement for supporting first-in-human studies [2]. However, increasing evidence has raised concerns about how accurately animal studies reflect human biology, prompting greater emphasis on the refinement, reduction, and replacement of animal testing with more predictive, human-relevant experimental systems[10].

2.3 Limitations of Animal Models in Drug Development

1. Species-Specific Biological Differences: One of the most critical drawbacks of animal models is the inherent biological divergence between animals and humans. Differences in genetics, metabolic pathways, immune responses, and receptor expression can substantially influence how drugs behave across species. As a result, compounds that demonstrate efficacy or safety in animals may fail during human trials, while others deemed unsafe in animals may later prove tolerable in humans. Such discrepancies contribute to false-positive and false-negative outcomes, thereby weakening translational predictability [10].

2. Limited Ability to Predict Human Toxicity and Clinical Efficacy Evidence from systematic reviews indicates that animal studies frequently fall short in forecasting human clinical responses, particularly in terms of toxicity and therapeutic benefit. Comprehensive analyses have shown that animal data successfully inform human clinical interventions only in a limited number of cases. Moreover, several toxicological outcomes, including carcinogenic and teratogenic effects, are often inadequately predicted by animal models, underscoring their restricted clinical relevance [11].

3. Artificial Nature of Disease Induction: Many animal disease models are generated through artificial induction techniques that may not accurately capture the complexity, duration, or variability observed in human diseases. For instance, experimentally induced inflammation or tumour models may oversimplify disease mechanisms and fail to represent the multifactorial nature of human pathology unless they are carefully aligned with clinical conditions. This lack of biological realism can distort assessments of drug efficacy and lead to misleading conclusions regarding disease progression and treatment response [12].

4. Methodological and Experimental Design Constraints: Preclinical animal studies are also affected by limitations in experimental design, including small cohort sizes, insufficient randomization, lack of blinding, and inadequate statistical rigor. In addition, external variables such as housing conditions, diet, and stress can introduce uncontrolled variability. Together, these methodological weaknesses reduce reproducibility and may partly explain the disconnect observed between promising preclinical results and subsequent clinical failure [12].

3. Organoids

Organoids are advanced three-dimensional (3D) cellular systems that develop through the self-organization of stem cells or primary tissue–derived cells. These miniature tissue models closely resemble real human organs in terms of structure, function, and genetic makeup. By reproducing key aspects of human tissue architecture, organoids effectively fill the gap between conventional two-dimensional (2D) cell cultures and animal models, offering a more physiologically relevant in vitro system [4, 14].

Because organoids maintain cellular diversity, organ-specific functions, and disease-related characteristics, they have gained significant attention as innovative tools for drug discovery, toxicity evaluation, and personalized therapeutic strategies [15].

3.1 Types of Organoids

Pluripotent Stem Cell–Derived Organoids

Organoids derived from pluripotent stem cells, including embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), are generated using controlled differentiation protocols that mimic developmental cues. These models are particularly useful for studying organ development, early disease mechanisms, and inherited genetic disorders [16].

Examples include:

- Brain organoids
- Liver organoids
- Intestinal organoids

Adult Stem Cell–Derived Organoids

Adult stem cell–derived organoids originate from tissue-resident stem cells and closely retain the biological and functional features of the donor tissue. This makes them especially suitable for modeling tissue-specific diseases and assessing drug responses that reflect patient biology [17].

Examples include:

- Intestinal crypt organoids
- Hepatic organoids
- Pancreatic ductal organoids

Tumour-Derived Organoids (Patient-Derived Organoids, PDOs)

Patient-derived organoids are established directly from tumour biopsy samples and preserve tumour-specific architecture, genetic alterations, and cellular heterogeneity. As a result, PDOs provide a powerful platform for individualized drug testing and therapeutic decision-making [18].

Key applications include:

- Screening anticancer drugs
- Studying drug resistance mechanisms
- Supporting precision medicine approaches

Organoids offer significant advantages in drug testing due to their ability to preserve three-dimensional architecture, correct cell polarity, and differentiated cellular states. These features enable drug responses that more closely resemble human in vivo physiology when compared with conventional two-dimensional culture systems[13,18]·In cancer research, organoids are particularly valuable because they maintain both inter-patient and intra-tumor genetic and phenotypic

heterogeneity, allowing for more accurate evaluation of therapeutic efficacy and the identification of drug resistance mechanisms[17,20].

Disadvantages

Despite their advantages, organoids also present several limitations that affect their broader application in drug discovery. Most organoid systems lack critical components such as vasculature, immune cells, neural inputs, and stromal elements, which restricts their ability to fully model complex organ-level interactions and systemic drug effects [21]. In addition, variability in extracellular matrices, including the use of Matrigel, as well as differences in differentiation protocols, can result in batch-to-batch inconsistencies and reduced reproducibility across laboratories [22]. Organoid culture techniques are also technically demanding, requiring specialized expertise, prolonged culture periods, and carefully optimized growth factor combinations, making them less accessible than traditional 2D models [23]. Moreover, their structural complexity and handling challenges limit scalability, reducing compatibility with high-throughput screening platforms commonly used during early stages of drug discovery [5].

3.2 Limitations of Organoids in Drug Testing

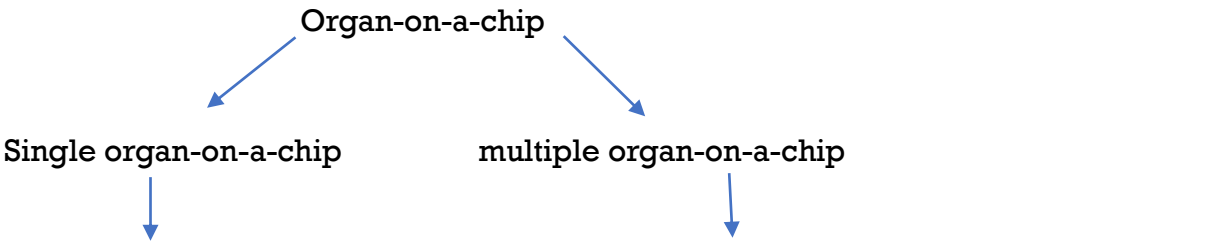
One of the major limitations of organoids in drug testing is their inability to replicate systemic pharmacokinetic processes such as absorption, distribution, metabolism, and excretion (ADME), which are critical for accurately predicting clinical drug behavior [25]. Although organoids offer improved tissue-specific toxicity assessment compared to traditional in vitro models, they do not adequately capture interactions between multiple organs, increasing the risk of overlooking off-target or systemic toxicities [3,25]. Additionally, the lack of a functional vascular network within most organoid systems results in uneven drug penetration, nutrient gradients, and the formation of hypoxic regions, all of which can complicate the interpretation of dose–response relationships [21]. Ethical considerations related to the use of human stem cells and patient-derived tissues further challenge organoid research, while the absence of standardized and universally accepted protocols limits regulatory approval and widespread adoption of these models [22].

4. Organ-on-a-Chip (OOC)

Organ-on-a-chip technology is a cutting-edge approach that integrates biological science with micro engineering to replicate key aspects of human physiology. These platforms consist of micro fluidic devices with networks of extremely fine channels, enabling precise manipulation of minute fluid volumes ranging from picolitres to millilitres. The term "organ" refers to the miniature, functional tissues cultivated within the chips, which can mimic specific physiological activities of human organs. Although these engineered systems are simpler than actual organs, they have been demonstrated to accurately model human biological

responses and disease processes. Organ-on-a-chip systems thus provide an advanced in vitro platform for studying living cells and tissues under tightly controlled experimental conditions [26].

4.1Types of Organ-on-a-Chip



1. Kidney-on-a-chip
   single chip
2. Lung-on-a-chip
3. Heart-on-a-chip
4. Artery-on-a-chip
5. Liver-on-a-chip
6. Intestine-on-a-chip
7. Brain-on-a-chip
8. Nerve-on-a-chip
9. Pancreas-on-a-chip
10. Placenta-on-a-chip
11. Skin-on-a-chip
12. Stomach-on-a-chip
13. Muscle-on-a-chip
14. Uterus-on-a-chip

4.2 Single-organ-on-a-chip

These platforms can closely replicate the physiological functions of native organs, making them highly effective for assessing the effects of individual compounds or complex chemical mixtures on specific organ systems [26]. They have been developed to model a variety of human organs, including the kidney, lung, heart, and liver, which are described in detail in the following sections [27].

1. Kidney-on-a-Chip

The kidneys are essential for waste excretion, fluid and electrolyte homeostasis, blood pressure regulation, and red blood cell production. Jang et al. developed the first multilayered micro fluidic platform to simulate renal filtration, initially using mouse kidney cells and later adapting the model to human cells. Musah et al. further advanced kidney-on-a-chip systems by recreating the glomerular capillary barrier and incorporating mechanical cues to mimic physiological conditions. These platforms are widely utilized for disease modelling, drug screening, and nephrotoxicity studies. For example, Kim et al. demonstrated that continuous infusion of gentamicin caused less nephrotoxicity than bolus dosing,

highlighting the value of kidney-on-a-chip models in pharmacokinetic and toxicological research [27].

2. Lung-on-a-Chip

Gas exchange in the lungs occurs in the alveoli, where oxygen and carbon dioxide are exchanged with the blood. Although replicating this process in vitro is challenging, lung-on-a-chip technology enables the creation of physiologically relevant pulmonary microenvironments. Huh et al. developed a lung-on-a-chip platform that mimics the alveolar–capillary interface, with alveolar epithelial cells in the upper chamber and pulmonary endothelial cells in the lower chamber. The system uses vacuum-induced cyclic mechanical strain to simulate breathing motions and allows the introduction of inflammatory stimuli, such as neutrophils. This platform serves as a robust tool for studying lung physiology, inflammation, and drug responses [27].

3. Heart-on-a-Chip

Micro fluidic heart-on-a-chip platforms provide advanced tools for studying cardiac tissue by utilizing cardiomyocytes (CMs), the functional units of the myocardium. Grasberg et al. developed a PDMS-based device in which the contraction of rat CMs caused membrane deflection, allowing precise measurement of contractile forces. Similarly, Marsano et al. designed a system that mimics the heart's physiological and mechanical environment by applying pressure to deform a membrane, simulating cardiac pumping. These heart-on-a-chip models are widely used to evaluate drug-induced effects on cardiac rhythm and cardio toxicity, playing a vital role in improving drug safety during development [27].

4. Artery-on-a-Chip

Artery-on-a-chip platforms provide a scalable and controlled micro fluidic approach for investigating intact small arteries and cardiovascular diseases. Günter et al. developed an organ-level micro fluidic system capable of loading, positioning, perusing, and super fusing delicate resistance artery segments while maintaining physiological temperature. The platform allowed precise spatial control of vascular stimulation and demonstrated localized vasoconstriction without propagation to adjacent regions. These models facilitate detailed analysis of arterial structure, endothelial and smooth muscle cell function, vascular tone regulation, and pharmacological responses. Additionally, other artery-on-a-chip systems have been applied to study carotid artery disease and abdominal aortic aneurysms using human endothelial and smooth muscle cells, highlighting their relevance in cardiovascular research and drug development [27].

5. Liver-on-a-Chip

The liver is the primary organ responsible for drug and toxin metabolism, organized into hepatic lobules composed mainly of hepatocytes that perform detoxification and biotransformation. Early liver-on-a-chip models, such as those

by Kane et al., demonstrated stable albumin production and drug-metabolizing activity in cultured hepatocytes. Subsequent platforms recreated the interstitial interface between liver sinusoidal endothelial cells and hepatocytes, enabling more accurate studies of substance exchange. Advances in micro fluidic design have also replicated the hexagonal architecture of hepatic lobules. Liver-on-a-chip systems are now extensively applied in drug discovery, toxicity testing, and disease modelling, including hepatitis B infection and alcohol-induced liver injury, underscoring their importance in pharmacological and pathological research [27].

Material	Sensor	Type of cell
Polycarbonate(PC)	Optical	Liver sinusoidal endothelial cells (LSECs).
Glass	PH	HepG2
Polymethyl methacrylate(PMMC)	Electrochemical	Hepatocytes
Alginates	-	Hepatocytes, Hepatic stellate cells, LSECs [27].

Table 1Liver-on-a-Chip: Key Materials, Sensors, and Cell Types

6. Intestine-on-a-Chip

The small intestine features villi that expand the surface area for efficient nutrient and drug absorption. Intestine-on-a-chip platforms are widely used to study oral drug uptake and interactions with the gut micro biome. Kim et al. developed a bilayer micro fluidic system separated by a porous membrane and lined with intestinal epithelial cells, enabling the investigation of drug transport and inflammatory responses under cyclic mechanical strain that simulates intestinal peristalsis. Additional models have successfully recreated aspects of the human duodenum and allowed co-culture of aerobic and anaerobic micro biota through controlled oxygen gradients. These intestine-on-a-chip systems offer significant potential for personalized medicine and micro biome-targeted therapeutic research [27].

7. Brain-on-a-Chip

The brain is a highly complex organ composed of diverse specialized cell types, making complete replication on a single chip challenging. As a result, brain-on-a-chip platforms typically focus on modelling specific neural compartments rather than the entire organ. These systems aim to reduce the time and cost of drug development for central nervous system (CNS) disorders. A major application is the modelling of the blood–brain barrier (BBB), which remains a critical obstacle in neurological drug discovery. Brain-on-a-chip models have been used to study BBB transport mechanisms, neuronal injury and axonal regeneration, myelination, and neurodegenerative diseases. Notably, micro fluidic platforms have provided

valuable insights into the cellular trafficking and accumulation of amyloid-β and Tau proteins associated with Alzheimer's disease, underscoring their importance in CNS research and drug development[27].

8. Nerve-on-a-Chip

Nerve-on-a-chip platforms address many limitations of traditional in vitro and animal models in predicting neurodegenerative outcomes and peripheral neurotoxicity. Due to the complexity of neuron–glia interactions, developing human-relevant peripheral nerve models has historically been challenging. Recent advances in nerve-on-a-chip technology integrate micro fabrication techniques with microelectrode arrays to record neuronal action potentials with high signal-to-noise ratios, enabling reproducible electrophysiological analysis. More advanced systems incorporate high-density CMOS-based microelectrode arrays and micro fluidic architectures to monitor axonal signalling at the single-axon level. Notably, a three-dimensional human peripheral nerve-on-a-chip model has demonstrated long-term culture stability, robust neurite outgrowth, and functional myelination, providing a compelling alternative to animal-based electrophysiological studies [27].

9. Pancreas-on-a-Chip

Pancreas-on-a-chip (POC) platforms offer advanced tools for studying pancreatic islet physiology and improving therapeutic approaches for diabetes. While insulin therapy remains the standard treatment for Type 1 diabetes, it does not fully replicate the dynamic regulation of pancreatic β-cells and carries a risk of hypoglycaemia. PoC systems enable standardized evaluation of islet quality, functional potency, and cellular clustering prior to transplantation, reducing ischemic and inflammatory damage. These micro fluidic platforms have also been applied to assess islet dysfunction in disease models such as cystic fibrosis, highlighting their potential in diabetes research and the development of cell-based therapies [27].

10. Placenta-on-a-Chip

Placenta-on-a-chip platforms are engineered to replicate the placental barrier, which regulates the exchange of oxygen, nutrients, waste products, and protective factors between the maternal and fatal circulations. Using micro fluidic technology, these systems reconstruct the multilayered architecture of the placenta with human trophoblasts, endothelial cells, and extracellular matrix components. Placenta-on-a-chip models allow controlled investigation of placental transport, metabolism, and barrier function under physiologically relevant conditions. By overcoming the limitations of conventional placental models, these platforms provide valuable tools for research in reproductive biology, toxicology, and maternal–feta medicine [27].

11. Skin-on-a-Chip

Skin-on-a-chip platforms are widely used for in vitro and ex vivo studies of skin permeability, irritation, toxicity, disease modelling, and the testing of pharmaceutical or cosmetic compounds. These systems employ reconstructed human skin, excised tissue samples, or synthetic membranes to examine dermatological and pharmacological responses under precisely controlled conditions. Skin-on-a-chip devices are generally classified into transferred systems, where skin biopsies or human skin equivalents are incorporated into micro fluidic platforms, and in situ systems, where skin tissue is engineered directly on the device. Advanced models integrating full-thickness skin with micro vascular networks provide more physiologically relevant assessments of systemic drug delivery and inflammatory skin disorders, such as atopic dermatitis, highlighting their significance in translational research and personalized medicine [27].

12. Stomach-on-a-Chip

Stomach-on-a-chip platforms address the limitations of conventional in vitro and animal models in replicating human gastric physiology and pathology. While three-dimensional human gastric organoids improve physiological relevance, accessing the luminal epithelial surface remains challenging. Microfluidic stomach-on-a-chip systems offer precise control over luminal flow, mechanical stimulation, and long-term maintenance of gastric organoids. These platforms enable targeted delivery of nutrients and drugs into the gastric lumen, simulation of peristaltic-like motions, and investigation of mucosal protection mechanisms. As a result, stomach-on-a-chip models are valuable tools for studying gastric function, disease processes, mucus–drug interactions, and drug discovery applications [27].

13. Muscle-on-a-Chip

Muscle-on-a-chip platforms provide physiologically relevant systems for studying skeletal muscle structure, function, and pharmacological responses. Skeletal muscle generates contractile forces essential for functions such as mastication and eye movement. Micro fluidic devices incorporating tissue-engineered skeletal muscle enable in vitro investigations of muscle development, injury, disease progression, and therapeutic interventions. Agrawal et al. developed a three-dimensional skeletal muscle-on-a-chip using photo patterned gelatin networks anchored to hydrogel pillars, promoting aligned muscle fiber formation and measurable force generation. This platform was employed to evaluate dose-dependent effects of cardio toxins on muscle architecture and contractile tension, demonstrating its utility in preclinical drug testing and musculoskeletal research [27].

14. Uterus-on-a-Chip

Uterus-on-a-chip platforms are engineered to replicate key functions of the female reproductive system, providing insights into reproductive physiology and infertility treatments. These micro fluidic systems can mimic critical aspects of the uterine microenvironment involved in ovulation, fertilization, and early embryonic development. Uterus-on-a-chip devices have been explored to overcome limitations of in vitro fertilization–embryo transfer (IVF-ET), such as low fertilization rates. Typical designs employ multilayer PDMS structures with porous membranes to support endometrial cell culture, along with micro fluidic channels for oocyte capture and nutrient delivery. These platforms offer valuable tools for advancing reproductive biology research and improving assisted reproductive technologies [27].

4.3 Multi-Organ-on-a-Chip

Single-organ-on-a-chip systems are limited in replicating complete human physiology because they lack inter-organ interactions. Multi-organ-on-a-chip, also referred to as human-on-a-chip, platforms seek to integrate multiple organ models on a single device connected through bionic blood channels, enabling the study of systemic physiological responses. Research has produced chips incorporating between two and ten organ types, such as liver–intestine models used to examine bile acid regulation. Pump less, user-friendly designs and high-throughput configurations have also been developed, although the complexity of the system increases with the number of integrated organs. These platforms offer a powerful tool for drug discovery and safety evaluation, allowing prediction of how liver metabolism and other organ functions influence systemic responses—capabilities that conventional 2D cultures and animal models cannot reliably provide [27].

Applications

Organ-on-a-chip technology is employed in pharmaceutical research to assess drug performance, metabolism, and safety using models that closely resemble human organs. These systems are widely used for toxicity screening, including liver, kidney, and heart toxicity studies.

OoC platforms also serve as effective tools for disease simulation, such as cancer, metabolic disorders, and inflammatory conditions. Moreover, by integrating cells derived from individual patients, these models contribute to personalized treatment strategies and allow evaluation of inter-organ drug interactions through multi-organ chip designs [28–32].

Advantages

OOC systems provide a more physiologically accurate environment than traditional cell culture techniques. They significantly reduce reliance on animal experiments and enable continuous observation of cellular responses under controlled conditions.

This technology enhances the prediction of human-specific drug effects and helps decrease the time and cost involved in drug development [29, 31, 33].

Disadvantages

Despite their benefits, organ-on-a-chip platforms face challenges such as high production costs and the need for advanced technical expertise. Maintaining stable, functional tissues for long durations is difficult, and current models cannot fully represent the complete complexity of human organs. In addition, regulatory frameworks for routine acceptance of OoC data are still under development [30, 33,34].

5. Role of Organoids

Organoids are three-dimensional (3D), stem cell–derived, self-organizing tissue cultures that closely resemble human organs at structural and functional levels. They comprise multiple organ-specific cell types arranged in a manner that partially recapitulates native tissue architecture and physiological functions, including contraction, endocrine secretion, filtration, and excretion [35].

Due to these characteristics, organoids have emerged as indispensable tools in contemporary biomedical research, particularly in drug discovery, disease modelling, and personalized medicine[36].

- **Drug Discovery and Screening**

Organoids provide physiologically relevant platforms for drug screening, enabling more accurate evaluation of drug efficacy than conventional two-dimensional (2D) cell cultures. Their 3D architecture supports realistic cell–cell and cell–extracellular matrix interactions, thereby enhancing translational predictability and improving the identification of promising drug candidates at early stages of development.

- **Drug Safety and Toxicity Assessment**

Organoids are widely applied in organ-specific toxicity testing, including hepatotoxicity, nephrotoxicity, and neurotoxicity assessments. The expression of functional drug-metabolizing enzymes and transporters within organoids allows improved prediction of adverse drug reactions (ADRs) during preclinical evaluation, thereby strengthening drug safety profiling.

- **Disease Modeling**

Organoids serve as powerful models for studying genetic disorders, infectious diseases, and cancer. Patient-derived organoids retain disease-specific genetic alterations and phenotypic characteristics, facilitating in-depth investigation of disease mechanisms and enabling assessment of therapeutic responses in a clinically relevant context.

- **Personalized Medicine**

Patient-specific organoids enable individualized drug testing and response prediction, supporting optimization of treatment strategies. This approach

advances precision medicine by guiding personalized drug selection and dosing while minimizing the risk of adverse effects.

- **Reduction of Animal Testing**

By generating human-relevant data, organoids offer effective alternatives to animal models, reducing ethical concerns and minimizing interspecies variability in drug response, thereby enhancing the reliability of preclinical findings.

- **Developmental and Regenerative Research**

Organoids contribute significantly to the understanding of organ development, cellular differentiation pathways, and tissue regeneration. These insights support progress in regenerative medicine, stem cell biology, and tissue engineering [35, 37].

6. Role of Organ-on-Chip Technology in Drug Safety and Toxicity Assessment

Organ-on-chip (OoC) technology is an advanced micro fluidic in vitro platform that incorporates living human cells within engineered microenvironments to replicate organ-level structure, function, and physiological dynamics[35].

Compared to traditional 2D cultures and animal models, organ-on-chip systems provide more predictive and human-relevant models for drug safety and toxicity evaluation [36].

- **Role in Drug Toxicity Assessment**

Organ-on-chip platforms enable precise assessment of organ-specific toxicity by simulating physiological conditions such as fluid flow, mechanical stress, and biochemical gradients. Liver-on-chip models are extensively used to evaluate drug-induced hepatotoxicity, as they exhibit functional drug-metabolizing enzymes and support long-term exposure studies. Similarly, kidney-on-chip, heart-on-chip, and brain-on-chip systems are employed to investigate nephrotoxicity, cardio toxicity, and neurotoxicity, respectively.

- **Prediction of Pharmacokinetics and ADME**

Organ-on-chip technology plays a vital role in studying drug absorption, distribution, metabolism, and excretion (ADME). Gut-on-chip models simulate intestinal absorption, while liver-on-chip platforms provide insights into metabolic pathways and metabolite-associated toxicity, enabling early identification of potentially harmful drug metabolites.

- **Chronic and Dose-Dependent Toxicity**

Unlike static cell cultures, organ-on-chip systems support continuous perfusion and long-term culture conditions, allowing evaluation of chronic toxicity, repeated-dose effects, and cumulative drug exposure—critical aspects of comprehensive safety assessment.

- **Multi-Organ and Systemic Toxicity Assessment**

Advanced multi-organ or body-on-chip systems interconnect multiple organ models, facilitating investigation of systemic toxicity, organ–organ communication, and drug–drug interactions. These platforms more closely replicate human systemic responses to pharmacological interventions.

Advantages in Drug Safety Evaluation

Organ-on-chip technology enhances the predictability of human toxic responses, reduces dependence on animal testing, and enables early identification of safety liabilities, thereby decreasing the likelihood of late-stage drug development failures[35-37].

7. Integration of Organoids and Organ-on-Chip Technologies in Pharmacovigilance and ADR Prediction

The integration of organoid and organ-on-chip technologies into pharmacovigilance frameworks represents a transformative approach to predictive adverse drug reaction (ADR) assessment and drug safety evaluation [38].Organoids, as 3D stem cell–derived mini-organ systems, closely mimic human tissue responses and provide more accurate assessments of drug metabolism and toxicity than traditional models, thereby improving early ADR prediction during preclinical development [39].

Organoid-based platforms, particularly those derived from liver and gastrointestinal tissues, generate critical data on drug absorption, metabolism, and toxicity that can be incorporated into pharmacokinetic and safety models to enhance translational relevance and reduce clinical failure rates. Complementarily, organ-on-chip systems recreate dynamic physiological environments through micro fluidic control of fluid flow, mechanical forces, and multi cellular interactions, enabling comprehensive toxicity profiling and identification of metabolite-induced adverse effects often overlooked in static cultures [40].

The ability of these platforms to support multi-organ interaction studies allows closer simulation of systemic drug responses, improving mechanistic understanding of ADRs and supporting proactive risk assessment. Furthermore, patient-derived organoids and personalized organ-on-chip models facilitate individualized ADR prediction, aligning with precision pharmacovigilance strategies and minimizing reliance on animal testing[38,39].

The synergistic application of organoids and organ-on-chip technologies enables integration of high-quality experimental data with computational ADR prediction tools and pharmacovigilance databases, enhancing early safety signal detection and validation prior to clinical exposure. Collectively, these human-relevant model systems establish a predictive and preventive paradigm for ADR assessment, strengthening both pre-marketing safety evaluation and post-marketing pharmacovigilance through early detection, mechanistic insight, and personalized risk stratification of adverse drug responses [39].

8. Challenges and Future Directions of Organoids and Organ-on-a-Chip

Challenges

Organoids are limited by inadequate vascular networks, variable reproducibility, and incomplete tissue maturation. Organ-on-a-chip models, although highly controlled, are constrained by technical complexity, material-related drug absorption, and insufficient regulatory standardization [41-43].

Future Directions

Advances are directed toward developing vascularized and immune-competent organoids, integrating multiple organs on a single chip, and creating hybrid organoid-on-chip platforms. These innovations aim to enhance physiological relevance and expand applications in drug discovery, toxicology, and pharmacovigilance [42–45].

9. Conclusion

Organoids and organ-on-a-chip technologies have emerged as powerful next-generation tools for preclinical drug evaluation, offering greater physiological relevance than traditional two-dimensional cultures and animal models. Organoids reproduce key aspects of human tissue architecture and cellular heterogeneity, enabling improved prediction of drug efficacy and organ-specific toxicity. Organ-on-a-chip systems further enhance translational accuracy by mimicking dynamic physiological conditions such as fluid flow and mechanical stress, while allowing assessment of systemic and inter-organ drug interactions. The combined use of these platforms strengthens early identification of adverse drug reactions, reduces dependence on animal testing, and lowers the risk of late-stage clinical failure. Although challenges remain, including technical complexity, limited standardization, and incomplete tissue maturation, ongoing advances such as vascularized organoids, multi-organ chips, and integrated hybrid systems continue to improve their applicability. Collectively, these technologies represent a promising and human-relevant approach for safer, more efficient drug development and modern pharmacovigilance.

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