

# Revolutionizing drug discovery and development: A comprehensive review of microfluidics in the pharmaceutical industry

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## ABSTRACT

The pharmaceutical industry has undergone a transformative paradigm shift in drug discovery and development, driven by the integration of microfluidic technology. Microfluidics is a considerably newer branch of science and technology that involves systems that use channels with sizes ranging from tens to a few hundred micrometers to process small ( $10^{-9}$  to  $10^{-18}$  l) volumes of fluid. In the past few decades, microfluidic technology has been predominantly used in biotechnology, including cloning and unit cell analysis. However, recent advancements in drug delivery technologies, along with the drawbacks associated with conventional methods, have gained the attention of scientists worldwide in the use of microfluidic technology in drug discovery and delivery. As a result, several products, especially point-of-care devices, have surfaced in the market in the last few years. According to Grand View Research, it is bound to grow with a compound annual growth rate of 12.19% from 2020 to 2030. In this review, we have attempted to provide comprehensive and up-to-date information about the fabrication, benefits, and application of microfluidics in the pharmaceutical industry. Despite the advantages, we acknowledge the challenges and have highlighted the recent advancements, their potential in drug discovery and development, and pandemic situations such as COVID-19.

## INTRODUCTION

Microfluidics is one such field that has seen tremendous growth in the past decade and has revolutionized various aspects of the pharmaceutical industry, including drug discovery, development, and analysis. This notable advancement is due to the development and exploration of technologies that help to analyze, manipulate, and move small quantities of fluid [1]. Microfluidics is a considerably newer branch of science and technology that involves systems that use channels with sizes ranging from tens to a few hundreds of micrometers to process small ( $10^{-9}$  to  $10^{-18}$  l) volumes of fluid [2]. In other words, microfluidics involves the strategic manipulation of fluids in a small-scale system that is competent in dealing

with the organic/biological environment at the microscale and throws light on a variety of cellular processes. This technology is used in various fields of the pharmaceutical industry, for instance, and has transformed how biologists examine cells and tissues by allowing them to conduct extremely precise experiments and evaluate biological samples with unmatched precision [3]. Microfluidics has transformed the way chemists synthesize and study molecules by enabling the execution of complex chemical reactions in a small, portable device. In the field of environmental monitoring, where it is being used to evaluate water, air, and soil samples with great precision and accuracy, microfluidics has also created new opportunities [4]. Microfluidics has transformed the way scientists investigate the behavior of fluids in the discipline of physics by enabling them to conduct experiments on small-scale systems that are not practical in bigger ones [1,5]. Among many applications, lab-on-chip (LOC), which is also referred to as the “micro-total analysis systems” (TAS) system, is the most prominent use of microfluidics technology [6]. The LOC technology has seen a dramatic development after the introduction of micro-electromechanical systems (MEMS) in the early 1990s owing to

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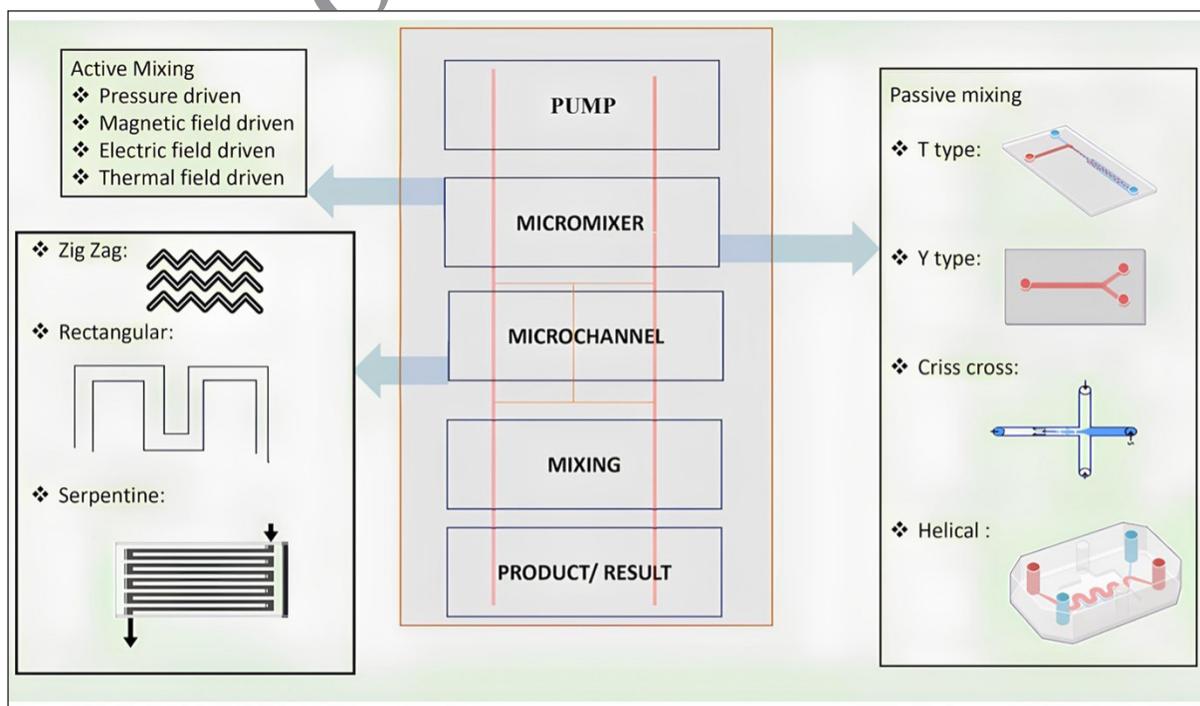
its huge potential in various fields, including diagnostic, point-of-care testing, medical, and a spectrum of other healthcare applications [7]. The primary goal of LOC technology at its inception was the downsizing of laboratory processes for handling fluids (gases and liquids). A collection of microfluidic devices, each with a specific purpose, such as controlling flow, mixing fluids, preparing samples, and detecting them on a tiny, miniaturized chip, make up an integrated LOC device. Due to its versatility, controllability, and scalability, LOC technology has attracted a lot of interest from the scientific fraternity [8]. Additionally, it could be effectively applied to the development of straightforward diagnostic systems and personalized medical care [9,10]. Our review mainly emphasizes on integration of operational parameter optimization using advanced design of experiment (DoE) approaches, as well as in-depth analytical performance evaluation specific to API detection. Additionally, while earlier literature primarily discusses fabrication techniques and basic applications, this review fills the gap by critically analyzing the interplay of device design, reaction conditions, and quantitative performance metrics, such as sensitivity, precision, and validation against standard methods. This comprehensive approach offers new insights and practical guidelines for optimizing paper-based microfluidic analytical devices, thereby advancing the field toward more reliable and efficient point-of-care applications.

## DESIGN AND FABRICATION OF MICROFLUIDIC SYSTEMS

The microfluidic system is inclusive of a wide array of devices that range from the simplest microneedles (MNs) used for drug delivery purposes to the complex organ-on-chip

(OOC) or LOC. The design, components, and technology used for fabrication vary based on the complexity of the system. In the preparation of simple microfluidics, just polymers along with drugs are sufficient to serve the purpose. For advanced systems, the number of components and critical parameters increases with an increase in the complexity of the device. While designing advanced systems, the mixing of the fluids inside the device is one important parameter that requires a lot of attention. In the case of several physical properties, such as heat and mass fluxes, as well as other chemical processes, the mixing phase is crucial [11]. The goal of mixing in microfluidics is to efficiently and quickly combine different samples at a very low volume (micro- or pico) scale to provide the largest possible interfacial area along with using the least amount of energy possible [12]. The overall efficiency of the mixing process can be enhanced by including baffles within microchannels carrying the fluid. In contrast to the inertial forces, viscous forces are more dominant in the capillary microenvironment. There are two major types of mixing processes, namely active and passive. Active mixing involves the use of an external agent such as temperature or magnetic field causing a disturbance in the flow of fluid resulting in efficient mixing [13]. Even though active mixing results in good mixing, it cannot be used always, especially while dealing with biological samples due to the stability problems arising from magnetic or electrical interventions [14].

In contrast to this, passive mixing uses the energy of the fluid flow to power the mixing process, which depends on the geometry of the microfluidic device along with other physicochemical aspects of fluid flow. As the sample passes along the microfluidic chip, the time and area with which the fluid is in contact are specifically specified within the microchannel



**Figure 1.** General components of a microfluidic system.

designs. Given that it increases the diffusion of the samples, passive mixing is regarded as an effective strategy for sample mixing [15]. There are two major types of flow designs one of which is T-junction channels and another Y-junction channels. Both have two different flow channels having fluids with/without solutes finally intersect at a point. The major difference between the two designs is that in the Y-junction channel, the two fluid channels intersect each other at an angle resulting in a sigmoid diffusion profile. Among the two designs, the T-junction design has been studied extensively. However, both the designs include following components (except in the case of microfluidics used in drug delivery). The general components of a microfluidic system are given in Figure 1.

## MICROFLUIDICS IN DRUG DISCOVERY AND SCREENING

Microfluidics has emerged as a breakthrough technique in drug discovery, modifying how researchers conduct tests and speeding up the drug development process. Microfluidic devices provide unparalleled control over experimental settings by manipulating small quantities of fluids within microscale channels and chambers, enabling high-throughput screening (HTS), precision dosing, and the production of physiologically realistic microenvironments for cells and tissues. This provides more precise and effective frameworks for different phases of the drug development pipeline, which have considerably aided drug discovery activities [16]. Microfluidics in HTS represents one of its most important contributions to drug development. Traditional drug screening methods are frequently time-consuming and arduous, whereas microfluidic devices can test numerous substances or conditions in tandem, substantially lowering experimental time and resource usage. This quick screening capability expedites the discovery of promising hit molecules and the initial phases of drug development [17].

### Microfluidics in drug delivery

Ideal therapy involves delivering the right dose of the drug at the correct site (target) at the correct time. Advances in microfluidic technology have enabled considerably increasing bioavailability as well as bioaccessibility along with reducing the side effects [18]. Using microfluidics, it is possible to develop a system with a high state of control and reproducibility. This technology is especially leveraged in the delivery of nanoparticles [19]. It allows accurate liquid management and rapid fluid movement in micrometer-scale channels. Microfluidic devices are employed for direct delivery of biologically active compounds in addition to the ability to create sophisticated drug carriers [20]. In this review, we have tried to explore two major applications of microfluidics in drug delivery.

### Drug carriers

#### Preparation for drug carriers

The ideal goal of incorporating drug carriers in therapy is to have greater control over the release rate and site and also to deliver the active ingredient at the desired site

thereby reducing the side effects and improving the overall efficacy of therapy [21]. In this regard, nanodrug carriers have gained attention of the scientists in this field. However, precise fabrication of such nanoparticles is a herculean task. This has resulted in researchers using microfluidic technology for the fabrication of nanocarriers from lipids, polymers, and inorganic materials [22]. Lipid-based nanoparticles have a structure that resembles that of a cell membrane and have been widely used in DDSs thereby having an array of advantages including biocompatibility, penetrating ability, simplicity of superficial modification, and considerably superior drug-loading capacity. The effectiveness of drug distribution and therapeutic efficacy is significantly influenced by the size of lipid-based nanoparticles. Conventional investigations, however, are hampered by the challenging procedures involved in creating liposomes because multiple steps after processing are necessary to keep liposomes homogeneous. To overcome these drawbacks, microfluidic platforms have drawn a lot of attention [23,24]. Microfluidic reactors as the name itself suggests are small in size; this, however, has restrictions that have limited its industrial utilization. These drawbacks include poor manufacturing rates, condensed equipment life, and high costs. Larger-scale reactions were required to overcome these obstacles. Formulation of nanoparticles using microfluidics technology is given in Figure 2.

#### A drug delivery device

The advent of microfluidic technology and different fabrication techniques have resulted in several drug delivery opportunities. Among all the available options, MNs top the hierarchy. Therefore, in this review, more focus is given to MNs as a drug delivery device [25]. MNs as the name itself signifies MNs involve micronized needles which are used especially for drug delivery purposes. In recent times, MNs have been combined with microfluidic devices for both drug delivery and analytical purposes [26,27]. There are different types of MNs which are given in the following.

#### Microneedles

Solid MNs: The use of solid MNs for pore-creating skin preparation was originally described in 1971. A sharp needle punctures the skin to administer medication through tiny channels that are then taken up by capillaries [26]. Easy medication loading and delivery mechanisms can be delivered by integrating solid MNs in microfluidic channels. These manufactured advanced devices have shown their utility as delivery vehicles using a variety of material chips and MNs consisting of silicon, tungsten, SU-8, and polydimethylsiloxane (PDMS) [28,29]. Coated MNs: As the name itself signifies these MNs include a drug coated over the miniature needles [30]. Different MNs used in drug delivery are given in Table 1.

Yeung *et al.* [31] developed a novel stereolithography-based 3D printing technique to fabricate integrated microfluidic-enabled hollow MNs in a single step. This approach overcomes previous limitations of high cost, low versatility, and limited throughput. The method achieves high-resolution printing beyond conventional limits, enabling the creation of complex microfluidic and MN architectures with enhanced efficiency.

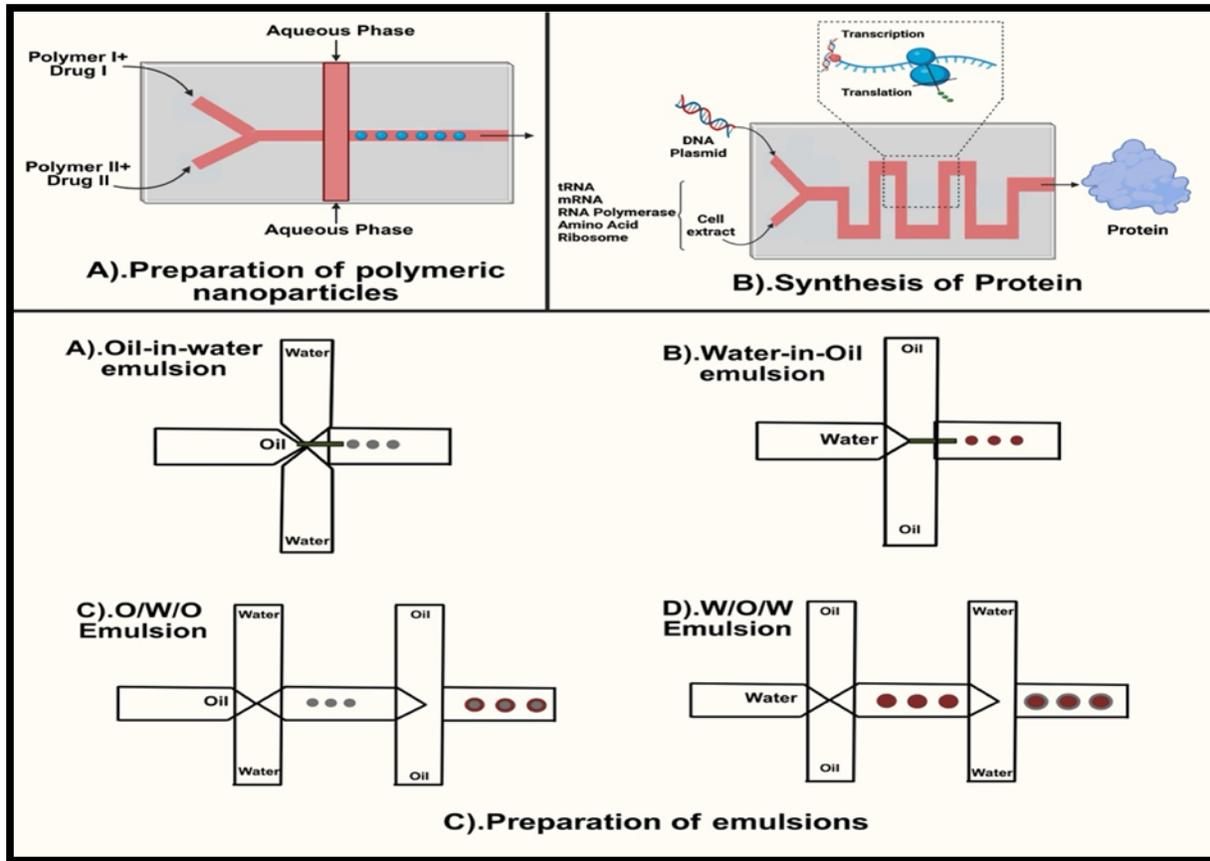


Figure 2. Formulation of nanoparticles using microfluidics technology.

Table 1. Different MNs used in drug delivery.

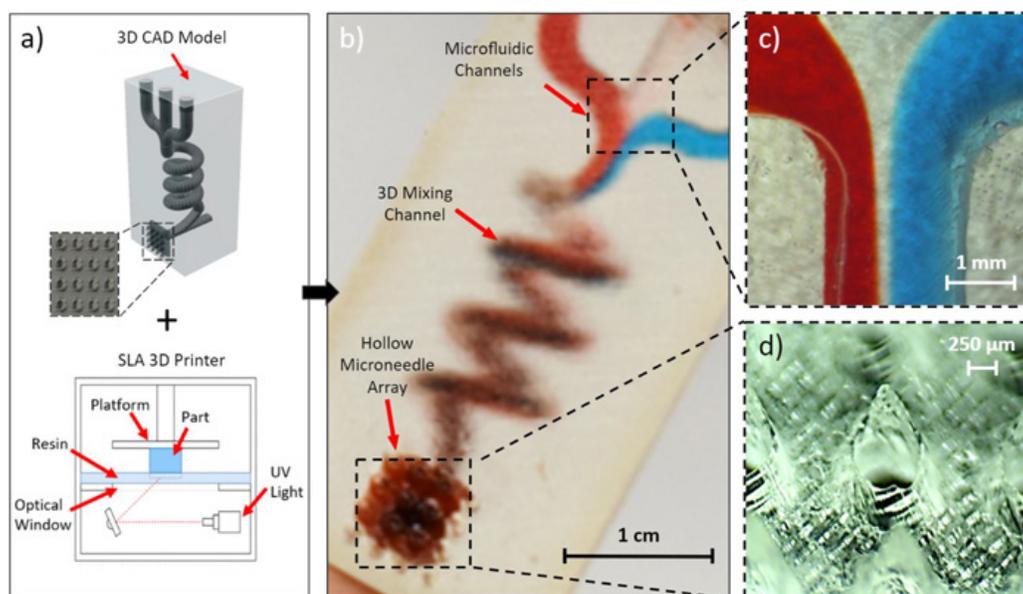
Sl.No	Microneedle Type	Method of preparation	Indication targeted	Drug delivery method	References
1	Solid MNs	Micro-molding Microfabrication	Hypertension Inflammation	Results microchannels in the biomembrane (skin) through which the drug is inserted	[32] [33]
2	Coated MNs	Microfabrication	In the detection of glucose by acting as a biosensor	Coating drug-load releases	[34]
3	Hollow MNs	3 D printing	As a localized injection for checking the effect of serotonin on heart rate	Pressure gradient flow through MNs	[35]
4	Dissolvable MNs	Photolithography	Treating Alzheimer's.	Dissolves on the applied area resulting in the release of drug load.	[36]

A prototype device demonstrated hydrodynamic mixing and transdermal drug delivery, showcasing the system's potential for advanced biomedical applications. These architectures offer promising capabilities for future transdermal therapies, including combinational drug delivery and preclinical testing of biologics, providing a customizable and cost-effective platform for innovative drug delivery systems. The drug delivery method using microfluidic-based MNs is depicted in Figure 3.

Mansor *et al.* [37] proposed a cost-effective and simplified method for cell detection using an integrated dual MN-microfluidic impedance flow cytometry system. This approach replaces conventional embedded electrodes with

removable tungsten MNs positioned at half the microchannel height, enabling efficient electrical impedance measurement of yeast cells. The reusable MNs simplify cleaning and reduce fabrication complexity and cost. Despite its low cost, the system effectively detects cells passing through the sensing zone, maintaining essential sensor functionality. This design offers a practical solution for medical diagnostics and food safety screening, especially in resource-limited settings, where affordability and ease of use are critical.

Trautmann *et al.* [38] presented a hybrid system integrating femtosecond laser-fabricated microfluidic channels with direct laser-written hollow MN arrays, aiming to develop



**Figure 3.** Drug delivery method using microfluidic-based microneedles. Reproduced with permission [31].

efficient point-of-care devices. Using a single laser system, MNs were produced through two-photon polymerization, and 3-dimensional microchannels were created in PMMA material. Compression tests confirmed that the MNs had sufficient strength for skin insertion. The unified fabrication method simplifies production by avoiding complex multi-step processes. A flow test using rhodamine B dye validated the system's ability for fluid injection and extraction. This integrated platform shows promise for painless drug delivery and lab-on-a-chip diagnostic applications in clinical settings.

## MICROFLUIDICS IN BIOANALYTICAL APPLICATIONS

In the past decade, rapid growth and continued research on microfluidics have brought about a revolutionary change in the field of bioanalytical sciences. This union of microfluidics with bioanalysis has given rise to a spectrum of cutting-edge uses that go beyond the limitations of traditional approaches [39]. Scientists have redefined the field of bioanalytical activities by unlocking new dimensions in precision, automation, and integration by utilizing the extraordinary capabilities of microfluidic systems. Microfluidics has established itself as a dynamic catalyst driving improvements in healthcare, diagnostics, and biological research. It has done this by developing small “lab-on-a-chip” platforms and streamlining complex sample preparation procedures [14].

### Lab-on-chip

Microfluidic platforms, also known as “lab-on-a-chip” devices, merge various analytical processes onto a unit microscale chip [40]. These tools are capable of carrying out operations such as sample preparation, separation, reaction, and detection in a very regulated and effective way. In the case of point-of-care diagnostics, where quick and precise analysis of small sample volumes is essential, lab-on-a-chip devices are

very useful [41]. A recent study by Pablo Rodriguez-Mateo *et al.* [42] explored LOC platforms by combining RNA extraction and SARS-CoV-2 detection processes. The lab-on-a-chip platform described in the work offers a promising alternative for resource-constrained environments. This cutting-edge technology accelerates the diagnostic process (470 pairs of genomic RNA per hour) while solving the infrastructure and skilled people issues that are frequently present in such situations. The platform improves efficiency and lowers the danger of contamination by combining two different steps one being sample preparation and the other involving detection in a single device. This development helps to manage and control the continuing epidemic in resource-constrained locations by speeding up the testing procedure and improving the accessibility of reliable SARS-CoV-2 RNA detection [42].

Murphy *et al.* created cellulose filter paper-based microfluidic paper-based analytical devices for the electrochemical detection of dopamine (DA) and ascorbic acid (AA) as well as chromatographic separation. They investigated the ion-exchange capabilities and physical characteristics of different filter sheets and discovered that these elements had a big impact on separation performance. VWR 413 accomplished baseline separation of AA and DA, but Whatman grade P81, a strong cation exchange paper, completely retained DA. The study showed that changes in ion-exchange capacity were caused by carboxyl groups on cellulose fibers. A DA detection limit of 3.41  $\mu\text{M}$  in the presence of 1 mM AA was achieved by enhanced resolution through eluent ionic strength and pH optimization, suggesting the device's potential for biological sample analysis [43]. Using chiral and reversed-phase columns, Lotter *et al.* [44] created the first chip-integrated 2-dimensional HPLC system for enantioselective micro-flow synthesis real-time monitoring. By facilitating heart-cut analyte transport between columns, this microfluidic system makes it possible to determine enantiomeric excess precisely

using mass spectrometry. The technology was shown to be faster and more efficient than conventional techniques in the asymmetric synthesis of warfarin. Despite the technological difficulties in integrating packed columns on-chip, this method combines reaction and analytical processes in a single device, offering extensive applicability for complex separations and advancing automated chemical synthesis. The first high-performance chiral liquid chromatography employing packed microfluidic glass chips has been demonstrated by Thurmann *et al.* Cellulose tris(3,5-dimethylphenylcarbamate) was packed into the chip-integrated columns using 5- $\mu\text{m}$  silica as the chiral stationary phase. The adaptability of the chip was demonstrated by the baseline separation of a variety of racemic substances, including medicines, into enantiomers under reversed-phase, polar organic, and normal-phase conditions. A lower plate height of 2.2 and better mass transfer at low retention were revealed by Van Deemter analysis. Ultrafast enantioseparations were accomplished in as low as 5 seconds using extremely short columns (down to 12 mm) [45,46]

### Organ-on-chip (OOC)

It is an emerging technology that has been in focus for the past several years as a result of a confluence of cell biology (stem cell) and microfluidics technologies [47]. The main goal of developing these systems is to simulate the physiological conditions of the host. In other words, these systems allow scientists to experiment *in vitro* (i.e., outside the living organisms) and still obtain results that relate to the host in the study [48,49]. The examples of novel OOC platforms include heart-on-chip, kidney-on-chip, bone-on-chip [50], lung-on-chip, and liver-on-chip [51]. Various *in vitro* models of cardiac diseases have been created using heart-on-a-chip technology. These models can be employed to investigate various disease mechanisms and treatment approaches. The most important elements of the heart that are responsible for keeping it pumping include cardiomyocytes (CMs), cardiac fibroblasts, and endothelial cells, among various other cardiac cells [52]. Since CMs beat rhythmically and react to various stimuli, such as external force and pulses of electricity, they are frequently employed as components of heart-on-a-chip devices [53].

None of the 22 research on bioprinting for OOC systems employed laser-based techniques: instead, 16 used extrusion-based bioprinting, 4 used inkjet, and 1 used stereolithography. Although extrusion-based bioprinting is simple to use and versatile with a range of biomaterials, it has drawbacks, such as nozzle clogging and low resolution. Only low-viscosity bioinks can be used with inkjet printing, which offers excellent resolution and cell survival. Although stereolithography guarantees excellent precision, the process is slow, and exposure to UV light may weaken cell viability. The biocompatibility, ECM mimicking, and printability of hydrogels—both natural and synthetic—make them popular bioinks for OOC applications [54,55].

The drawbacks of non-vascularized organoids, which frequently experience inadequate oxygen supply and waste accumulation that results in necrosis, are being addressed by vascularized OOC models. OOCs improve drug screening and disease modeling by more accurately simulating *in vivo* tissue

conditions with the integration of microvascular networks. Research on metabolism and toxicity is aided by liver-on-a-chip systems, which coculture hepatocytes with endothelium and other liver-specific cells in a perfusable microenvironment to imitate liver function and structure. While heart-on-a-chip devices use CMs derived from induced pluripotent stem cells to replicate the myocardium, allowing for drug testing and modeling of heart conditions, vascularized lung-on-a-chip models replicate the alveolar-capillary interface, which is useful in the study of respiratory infections, such as COVID-19. Additional examples include neurovascular units for researching the blood–brain barrier and vascularized bone marrow and kidney chips for nephrotoxicity and cancer research.

These systems offer platforms that are physiologically appropriate and help close the gap between intricate *in vivo* models and conventional 2D cultures. Gut-on-chip model microfluidic device is depicted in Figure 4 [56]. In addition, different types of microfluidic designs consisting of different organ models are given in Table 2.

### Integration of OOC with AI

OOC technology and artificial intelligence (AI), especially deep learning (DL), are fast-evolving technologies with high potential when combined, especially for drug evaluation. OOCs represent great preclinical models but are hindered by limitations in scalability and throughput, which restrict their general application to drug screening [57]. Recent advancements involve high-throughput microfluidic platforms where experiments can be conducted in parallel with real-time sensing and imaging, and large datasets are produced. Examples include devices with 36 to 384 devices to model sophisticated tissues and disease conditions, greatly expanding experimental capacity and data quantities [58].

However, processing and analyzing this massive amount of data become a labour-intensive and time-consuming task, which leads to a snag in data interpretation. AI—more especially, machine learning and DL—can help automate data analysis, reduce human bias, and accelerate insights. Without the need for explicit software coding, machine learning (ML) uses supervised, unsupervised, semi-supervised, and reinforcement learning techniques to identify patterns and provide predictions. As a branch of machine learning that uses deep neural networks, DL excels at processing raw, complex data to extract features more accurately and efficiently. In order to reduce computing demands, transfer learning in DL also makes it easier to reuse previously trained models for related tasks. With the integration of high-throughput OOCs and AI, scientists are able to efficiently process large multidimensional data sets, enhancing drug discovery and testing protocols. The fusion is accomplished through accurate measurement equipment, stable data acquisition and storage infrastructure, sophisticated ML software for data retrieval, and insightful result interpretation. This combination holds the potential for better, faster, and more scalable drug development pipelines that can revolutionize pharmacological studies, particularly for complicated drugs and personalized medicine [59,60].

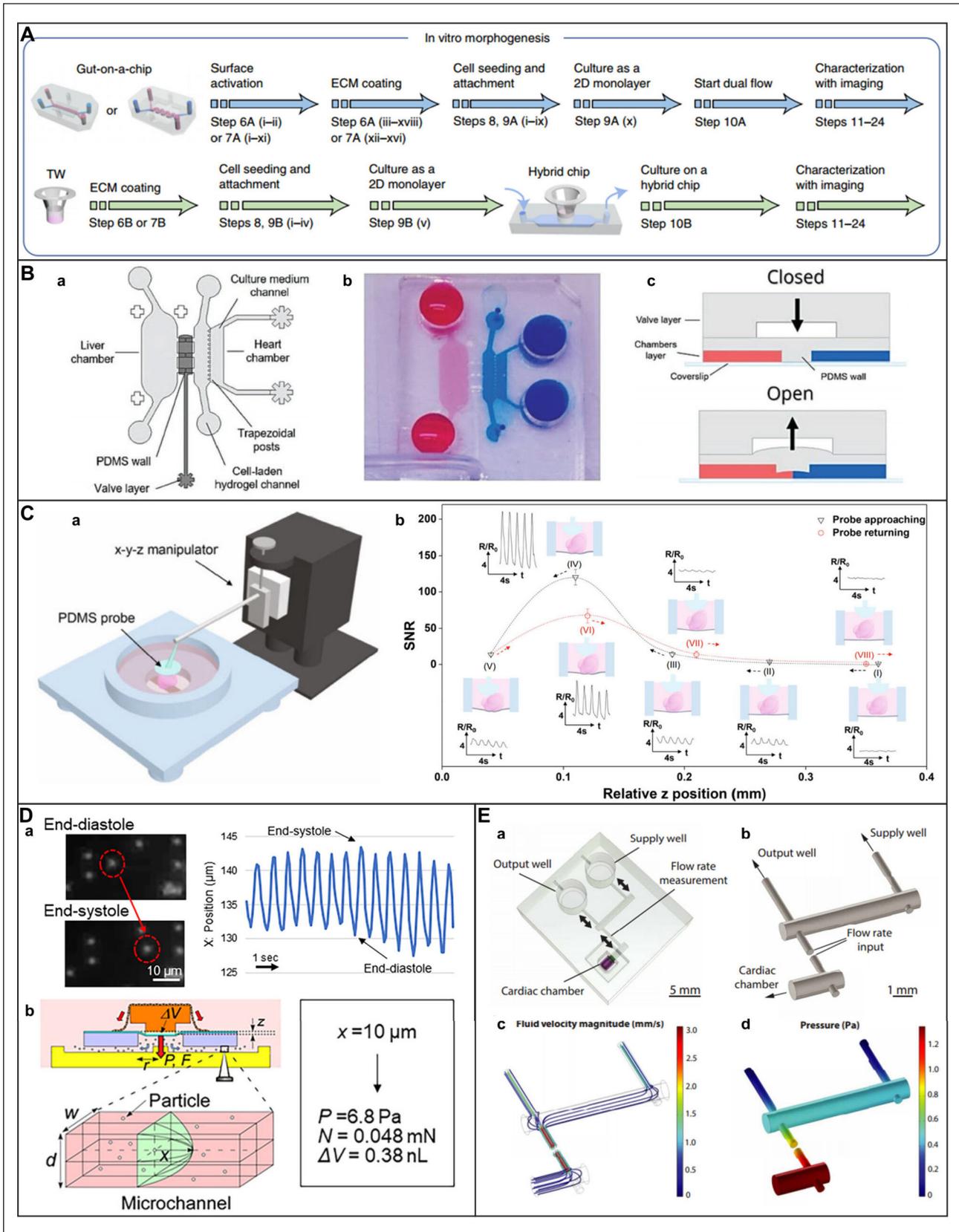


Figure 4. Gut on chip model microfluidic device. Reproduced with permission [56].

**Table 2.** Different types of microfluidic design consisting of different organ models.

Organ model	Cell type used	Microfluidic design	Key findings	References
Liver	Primary human hepatocytes, HepG2 (human hepatocellular carcinoma cells), HUVECs (human umbilical vein endothelial cells)	Foldable, layered paper/polyimide-based microfluidic chip integrated with nanoporous membranes	Origami-based liver-on-a-chip shows easy fabrication, good cell viability, and effective drug toxicity testing.	[63]
Lung	HepG2 cells  A549 (lung cancer), RFP-A549 (red fluorescent protein-transfected lung cancer), HFL-1 (fibroblasts), and L02 (human normal liver cells)  Human umbilical vein endothelial cells (HUVECs), lung fibroblasts (LFs), A549 lung cancer cells	PDMS-based microfluidic chip mimicking hepatic lobule was fabricated using soft lithography and modified with APTES-PDA for hydrogel adhesion.  A multilayer PDMS-based microfluidic chip with gas, fluid, isolation, and chamber layers bonded to a glass substrate, designed for 3D cell culture and gas-liquid diffusion.	A liver-on-chip with a continuous microvascular network was developed using HD laser patterning, enabling drug delivery studies and liver function assessment.  The 3D-CMOM platform effectively models lung cancer liver metastasis under controlled oxygen levels, identifies key metastasis pathways, and enables screening of hypoxia-targeted anticancer drugs.	[64]
Kidney	Human embryonic stem cells (H9), H9-derived PKHDI mutants, and ARPKD patient-derived induced pluripotent stem cells (iPSCs)	PDMS  Millifluidic chip	3D printing and capillary pinning enable high-throughput microfluidic devices with thin hydrogel layers suitable for cell culture and imaging, supporting future cancer models and drug screening.  The kidney organoid-on-a-chip model accurately replicates ARPKD pathology, identifies RAC1 and FOS as key drivers of cystogenesis, and demonstrates the therapeutic potential of R-naproxen and T-5224 for clinical translation.	[65]
Heart	The cell line used is PTEC-TERT1 (ATCC CRL-4031), an immortalized human proximal tubule epithelial cell line.  Poly(methylmethacrylate) (PMMA) or polystyrene using CNC milling, incorporating PDMS rods (~210 µm diameter) fabricated by curing PDMS  Microgroove-patterned PDMS-based chip integrated with a gold electrode array	The chip used is a multiplexed chip device (MCD) made of polycarbonate, designed to support six individually addressable and perfusable 3D OPTEC-on-chip models.  Human ventricular cardiac fibroblasts, human-induced pluripotent stem cell-derived CMs (hiPSC-CMs), specifically iCell lines A and B  The cell line used in this study is primary neonatal rat ventricular CMs, isolated from 1–3-day-old Sprague–Dawley rats.	Developed a perfusable 3D organoid-derived proximal tubule-on-chip model with enhanced transporter expression, drug uptake, and nephrotoxicity prediction.  A human cardiac fibrosis-on-a-chip model was developed that mimics disease features and shows pirfenidone reduces fibrosis markers but not contractile loss.  A scalable heart-on-a-chip with microgrooves and electrodes enables rapid preclinical drug screening using mature cardiac microtissues, adaptable to various cell types.	[66]
				[67]
				[68]
				[69]
				[70]

## Emerging frontiers (2024–2025)

### Microfluidic rheology

Zsófia Vilimi *et al.* studied the viscosity of various pharmaceutical products such as gel, solutions, injections, and excipients using two instruments: the Kinexus Pro<sup>+</sup> rotational rheometer and the Fluidicam<sup>TM</sup> RHEO microfluidic viscometer. These were selected based on the formulation type and route of administration. The Kinexus Pro<sup>+</sup> measured flow properties across a broad viscosity range (1 mPa.s to 10,000 Pa.s) using cone–plate or plate–plate geometries, with shear rates and temperatures adjusted to simulate actual usage conditions. The Fluidicam<sup>TM</sup> RHEO, ideal for fluid or shear-thinning semisolid formulations, used laminar flow and reference liquids (5, 50, 500 mPa.s at 25 °C) to determine viscosity, particularly under high shear conditions such as blinking or injection. Nozzle and applicator dimensions were measured using a digital caliper ( $\pm 0.02$  mm accuracy) to estimate shear rates during application. Extrudability was assessed using a handheld hardness tester to determine the force needed to dispense vaginal gel: Klyisma. Shear stress and shear rate calculations were based on standard fluid mechanics equations considering viscosity, flow rate, nozzle size, and applied force. The results revealed that the rotational rheometer works well for gel-based formulations across a wide shear range but is less effective for low-viscosity samples. It allows partial sample recovery. The microfluidic rheometer suits high-shear applications such as injections and eye drops but is destructive. Both methods gave similar results in overlapping ranges, with the microfluidic device offering faster analysis and minimal preparation. Each method has specific uses and benefits [61].

### Modular microfluidic chip

Lambert *et al.* [62] investigated the polymorphic forms of drugs including Rimobant, Sulfathiazole, Aripiprazole, and Irbesartan using a custom-built microfluidic platform. The setup includes components for droplet generation, temperature control, and real-time characterization via UV, optical microscopy, and Raman spectroscopy. Saturated drug solutions are prepared by flowing solvent through a powder-filled column, and droplets are formed using a fluorinated oil. Droplets are cooled to induce crystallization, and their polymorphic forms are analyzed. The platform uses chemically resistant materials and 3D-printed holders. Interfacial energy is measured by the pendant drop method, with solubility also confirmed using traditional millivials. Solubility and crystallization of Irbesartan, Rimobant, Aripiprazole, and Sulfathiazole were studied using microfluidics. Results showed form-specific solubility differences, phase transitions, and nucleation influenced by cooling rates and solvents. A new Sulfathiazole polymorph (U1) with unique properties was discovered, highlighting microfluidics' effectiveness for polymorph screening.

### Instant topical drug quantification with 3D microfluidics

Benjamin A. Kuzma *et al.* investigated the permeability of Ruxolitinib formulations by applying it onto the mouse ear skin using a 3D-printed applicator. Stimulated Raman scattering microscopy was employed to

track the drug penetration over 2 hours. Drug concentrations in lipid-rich and lipid-poor skin regions were analyzed, and pharmacokinetic parameters were compared using statistical tests. The study developed a 3D-printed applicator enabling precise, low-volume (20  $\mu$ l) topical drug delivery and real-time imaging of early drug permeation into mouse skin. The study revealed that PEG enhanced rapid drug uptake, while DGME provided sustained release, highlighting formulation impacts on skin pharmacokinetics and potential for screening excipients [71].

### Flexible microfluidic sensor

Ractopamine is illegally used in food, which can harm health, so quick and low-cost testing is needed. The study developed a cost-effective colorimetric chemosensing platform using modified paper-based microfluidic devices (mPCD) and various gold nanoparticles (AuNPs) to detect ractopamine (RAC) in chicken meat. Four types of AuNPs—AuNPs-CysA, AuNPs-DDT, positively charged AuNPs, and gold nanostars (GNSs)—were synthesized, with AuNPs-CysA and AuNPs-DDT showing significant colorimetric changes upon RAC interaction. The device design included hydrophilic and semi-hydrophilic zones formed by paraffin treatment. Characterization via FE-SEM, TEM, AFM, EDS, UV-Vis, and zeta potential confirmed the successful synthesis and stability of AuNPs. The Instant Eyedropper tool and Colorxs software were used for digital color analysis, enhancing detection accuracy. The sensor with cysteamine showed good detection from 0.1 mM to 0.01 M with a detection limit of 0.001 mM. Another sensor with dodecanethiol was even more sensitive, detecting as low as 1 nM. These sensors were easy to make, stable, and worked well. Finally, the system was combined with a simple glass fiber device to allow on-site food testing [72].

## CHALLENGES AND LIMITATIONS OF OOC

It is inherently difficult to accurately replicate the multilayered architecture and multifunctionality of human tissues. Each organ has a unique cellular composition, mechanical property, and microenvironment that is hard to reproduce *in vitro*. Compounding the issue of complexity, there is the requirement to physically replicate the size and number of cells in each organ to reach physiologically relevant levels; this is important to produce meaningful experimental results. A common and routine fabrication method used in the development of OOC devices is soft lithography; this requires cleanroom facilities and specialized equipment that do not exist in all laboratories. Moreover, even alternative, lower-resolution methods of fabrication still add complexity when integrating parts and the combined assembly and operations of devices. PDMS remains widely accepted as a material for OOC devices; however, PDMS has limitations including adsorption of hydrophobic drugs, leaching of uncrosslinked oligomers, and restrictions on the dimensions within the channels; each of these factors can affect experimental outcomes and drug testing reliability. As substitute materials, such as PMMA

polymers, are developed and has unique fabrication and performance benefits

## CONCLUSION

This review paper explores the field of microfluidics, a technology that involves controlling the flow of fluids at the microscale. We delve into various methods used to fabricate complex mPCD, including photolithography, soft lithography, and 3D printing. The underlying principles of microfluidics are discussed, with a focus on the unique characteristics of fluid behavior at the microscale, such as the dominance of surface tension and laminar flow. Recent advancements in microfluidics are highlighted, including the integration of microfluidics with other technologies such as optics, electronics, and nanotechnology. These advancements have led to innovative applications in diverse fields, including drug delivery, diagnostics, environmental monitoring, and energy production. As the field continues to progress, future research efforts will likely focus on developing scalable, cost-effective, and user-friendly microfluidic systems. Overcoming challenges related to scalability, cost, and user experience will be crucial to fully harness the potential of microfluidics. With ongoing innovation and interdisciplinary collaborations, microfluidics is poised to revolutionize various industries and improve our quality of life.

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## AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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The author reports no financial or any other conflicts of interest in this work.

## ETHICS APPROVAL

This study does not involve experiments on animals or human subjects.

## INFORMED CONSENT

This review has not involved studies on the human participants.

## DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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