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Review

Beyond Polydimethylsiloxane: Alternative Materials for Fabrication of Organ-on-a-Chip Devices and Microphysiological Systems

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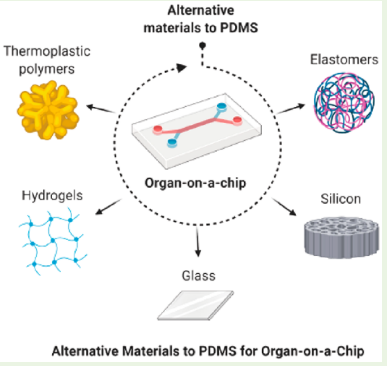
ABSTRACT: Polydimethylsiloxane (PDMS) is the predominant material used for organ-on-a-chip devices and microphysiological systems (MPSs) due to its ease-of-use, elasticity, optical transparency, and inexpensive microfabrication. However, the absorption of small hydrophobic molecules by PDMS and the limited capacity for high-throughput manufacturing of PDMS-laden devices severely limit the application of these systems in personalized medicine, drug discovery, *in vitro* pharmacokinetic/pharmacodynamic (PK/PD) modeling, and the investigation of cellular responses to drugs. Consequently, the relatively young field of organ-on-a-chip devices and MPSs is gradually beginning to make the transition to alternative, nonabsorptive materials for these crucial applications. This review examines some of the first steps that have been made in the development of organ-on-a-chip devices and MPSs composed of such alternative materials, including elastomers, hydrogels, thermoplastic polymers, and inorganic materials. It also provides an outlook on where PDMS-alternative devices are trending and the obstacles that must be overcome in the development of versatile devices based on alternative materials to PDMS.



Alternative Materials to PDMS for Organ-on-a-Chip

KEYWORDS: *biomaterials, organ-on-a-chip, microphysiological systems, drug testing, microfabrication, PDMS-free, hydrogels, elastomers, glass, silicon, thermoplastic polymers, polydimethylsiloxane*

INTRODUCTION

Organ-on-a-chip devices and microphysiological systems (MPSs) establish precisely controlled, dynamic microphysiological environments to support the growth and function of human tissues with the intention of recapitulating their *in vivo* counterparts, often utilizing perfusion to mimic vasculature.[1] A plethora of devices have been engineered for a wide range of organs and the study of more complex multiorgan systems has significantly increased in recent years.[2,3] These studies often aim to validate the capacity of these tissues to function and mimic simplified *in vivo* tissues, screen for drug toxicity with these tissues, or both. These organ-on-a-chip devices and MPSs thus can act as promising alternatives to standard animal and *in vitro* models, providing a potential solution to the consistent increase in the cost of drug development.[1] Recent advances in induced pluripotent stem cell (iPSC) biology have afforded the cultivation and expansion of patient-specific cells,[4,5] opening the door to personalized MPS-based drug screening and treatment assessment. Further, as multi-organ-on-a-chip technologies advance, the field is edging closer to *in vitro* adsorption, distribution, metabolism, and elimination (ADME) modeling that can effectively mimic the pharmacokinetic/pharmacodynamic (PK/PD) conditions of an active pharmaceutical ingredient (API) *in vivo*.[6−8]

Polydimethylsiloxane (PDMS) was crucial in the majority of the early seminal work in the organ-on-a-chip field[9] and remains a prodigious material for MPSs; the majority of devices still utilize PDMS as their primary structural and cell-interacting component.[1,3] This is because PDMS has several beneficial properties, including its low-cost; ease of use in soft lithography; optical transparency for cell imaging and assessment; high elasticity allowing for on-chip cell manipulation; and good oxygen permeability and biocompatibility for long-term cell culture in enclosed microfluidic channels or chambers.[10] Its widespread use is also attributed to the fact that PDMS can be used to fabricate flexible membranes and microfluidic channels, which can recapitulate mechanical tissue strain, native tissue elasticity, and induce cell orientation through topological cues.[11] However, PDMS also has several drawbacks that are encouraging a transition to alternative materials as the MPS field progresses toward increasingly advanced systems that can mimic *in vivo* cell−drug interactions and PK/PD profiles more effectively.

It is well established that PDMS readily absorbs small hydrophobic molecules, including compounds added to culture

Special Issue: Beyond PDMS and Membranes: New Materials for Organ-on-a-Chip Devices

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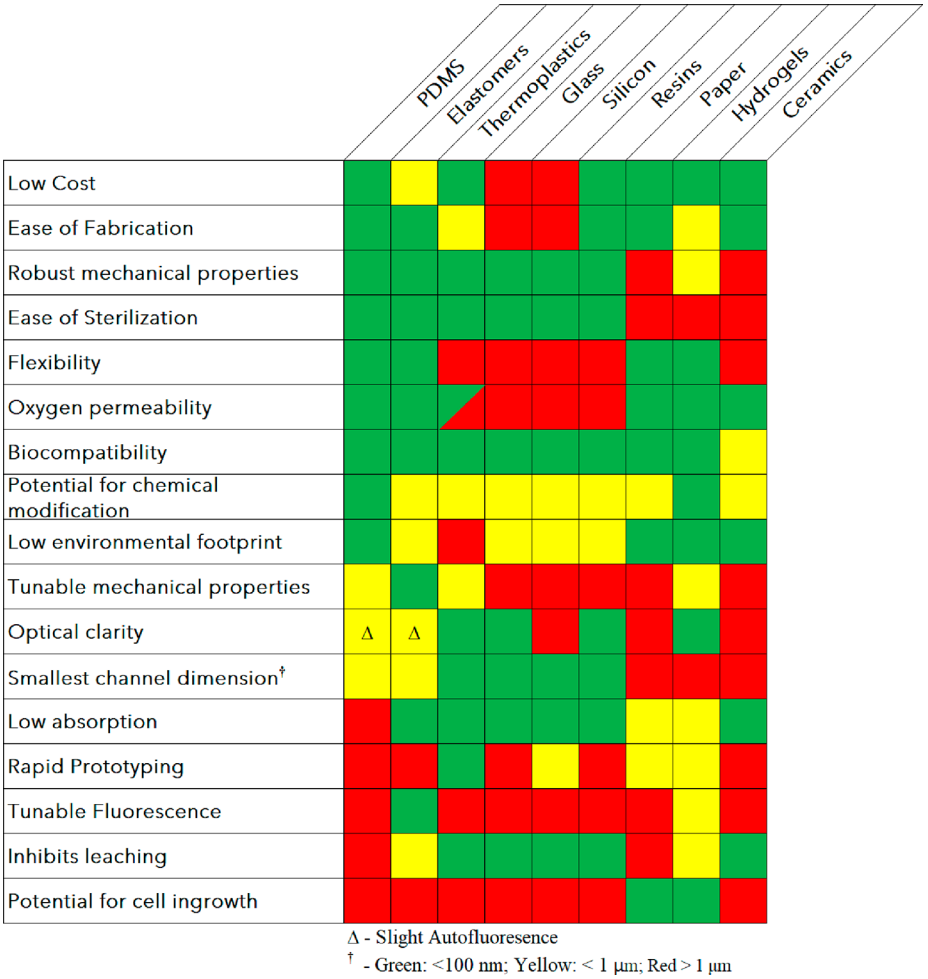
Table 1. General Comparison of Various Material Considerations for Organ-on-a-Chip Devices and MPSs between PDMS and Alternative Device Materials[a]



[a]Green, yellow, red indicate generally positive, moderate, or negative characteristics, respectively.

medium, cell signaling compounds, and the therapeutics often being assessed in cell−drug interaction studies.[11−15] Consequently, the use of PDMS-based devices can result in misrepresentations of drug toxicity and efficacy. The accuracy of the observed drug interactions and PK/PD models of these systems is inherently limited, or, if the PDMS absorption of the moiety of interest is estimated/modeled for,[7] require a significant amount of additional work to be invested.[10,11] For microfluidic MPSs, the PDMS channel surfaces can be chemically modified (with materials including polydopamine and polynorepinephrine[16]) to minimize absorption, but such coatings must maintain their stability over the course of experimentation, which may last several weeks.[10,11,17,18]

PDMS is also slightly autofluorescent,[13] causes Raman scattering,[19] is incompatible with organic solvents,[17] and is gas permeable.[17] Gas permeability is a benefit in certain cases but can lead to evaporation and alterations in medium composition, bubble formation, the inability to culture anoxic cells, and variations in osmolarity.[20,21] The oligomers that encompass PDMS also have the potential to leach out, resulting in deformation or potential issues in cell culture.[20,22] Notably, the soft-lithography process of many PDMS-based devices requires master molds that take time to develop. This less efficient technology presents significant difficulties for rapid prototyping and transitioning to large-scale, high-throughput industrial manufacturing, a necessity for drug discovery strategies.[1,20,23]

The similarities between the manufacturing methods, materials, and length scales of these organ-on-a-chip devices and MPSs and the more established field of microfluidics signify that materials-focused microfluidics review articles[24,25] are highly relevant for organ-on-a-chip devices and MPSs. Indeed, many of the manufacturing, operating, and materials-related challenges, lessons learned, and breakthroughs of the two fields are inherently linked. For example, the impact of nonspecific absorption and adsorption has a considerably greater influence at the length scale of microfluidic channels where the surface-to-volume ratio is large.[24] Just as this is a persistent concern in microfluidics, it is also a significant issue in organ-on-a-chip devices and MPSs where this large surface-to-volume ratio that relates to both adsorption of proteins in media-laden channels and absorption of drugs, so utilizing alternative materials that experience less drug absorption than PDMS is of enhanced importance at the length scales of these devices.

The gradual shift toward the use of alternative materials to PDMS for organ-on-a-chip devices and MPSs is an acknowledgment that PDMS, while clearly useful for a wide range of

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Table 2. Definitions of Materials Considerations for Building Successful Organ-on-a-Chip and MPS Models

low cost	Less expensive materials lead to cheaper lab-scale prototyping and better commercial potential at larger scales.
ease of fabrication	Simpler fabrication strategies are highly advantageous, particularly when considering the potential for producing devices at mass scales. This is generally related to the manufacturing methods of the material, but the material properties themselves can have an influence on the processability of a material (e.g., lower melting temperatures (T_m) and glass transition temperatures (T_g) often afford better processability for thermoplastic materials).
robust mechanical properties	This generally refers to the Young's modulus of the material. Stronger materials will retain their original dimensions throughout experimentation, providing consistency for the operation of the device and cells. Stiff materials generally do not mimic cellular environments, and materials that are too stiff can be detrimental for the effective culture and maturation of dynamic cells, such as heart and lung cells.
ease of sterilization	An effective, easily accessed means of sterilization of the devices allows for a lesser delay between device fabrication and use and could lower costs substantially during commercialization.
flexibility	Flexible materials can promote the effective culture and maturation of dynamic cells through improved recapitulation of mechanical tissue strain and native tissue elasticity. Flexible materials may also induce cell orientation through topological cues.
oxygen permeability	Generally, oxygen permeability is desired for the culture of a wide range of cell types and to avoid bubble formation within devices. However, lack of oxygen permeability may be desired for the culture of anaerobic cells or studies in which finely controlled oxygen levels are desired.
biocompatibility	All materials should be biocompatible to effectively promote cellular growth.
tunable mechanical properties	The ability to tune the mechanical properties of a material can be used to develop materials that better mimic the cellular microenvironment or to allow for adjustments that can achieve improved cellular maturation.
optical clarity	Optical clarity is essential for real-time observation and assessment of cells/cellular characteristics. Autofluorescence may affect such observation.
smallest channel dimension	Higher resolution within the design can afford more precise structures and potentially better control over fabricating various topologies within the device.
potential for chemical modification	Chemical modifications can be used to alter surface charges and hydrophilicity to further limit adsorption on the device.
environmental footprint	The life cycle of the materials used in the device should be considered. This factor relates to whether these materials degrade into environmentally safe byproducts (although the method of production should be a consideration as well).
low absorption/adsorption	Small molecule absorption significantly limits the application of devices in personalized medicine, drug discovery, in vitro pharmacokinetic/pharmacodynamic (PK/PD) modeling, and the investigation of cellular responses to drugs.
rapid prototyping	For the sake of this article, rapid prototyping relates to the time required to develop an entirely new design to test in the lab. If, for example, this would include the development of a new master mold via stereolithography, which takes time (generally in clean room facilities), that is not considered rapid prototyping here.
tunable fluorescence	This may be desired to view and assess the mechanics of dynamic cells within specific locations of the device.
inhibits leaching	Leaching of materials from devices can result in device deformation or potential negative effects in cell culture and should be limited.
potential for cell ingrowth	Cell ingrowth is essential for materials designed to directly contact the cultured cells and recapitulate their native extracellular environment.

Table 3. Comparisons of Three Alternative Elastomers Used for Fabricating Microfluidic Devices

property	polyester elastomers	tetrafluoroethylene-propylene (FEPM) elastomers	thermoplastic elastomers
optical clarity	good	good	good
mechanical properties	soft to moderate (e.g., PICO polymer 3: Young's modulus of 678 ± 67 kPa[30])	soft to moderate (e.g., Young's modulus of 0.8 MPa[31])	moderate to robust (e.g., Kraton G1643, Young's modulus of 33.85 ± 3.05 MPa[32])
hydrolysis resistance	excellent	excellent	excellent
fabrication methods	template molding	compression molding	injection molding hot embossing
suitability for scalable manufacturing	fair	good	excellent
advantages	• low fabrication cost • tunable mechanical properties • low absorption	• excellent chemical resistance • low absorption	• low fabrication cost • recyclable/reprocessable • tunable elasticity • low absorption • simple and fast bonding
limitations	• incompatible with organic solvents • difficult for mass production	• poor extrusion resistance • relatively expensive	• poor resistance in specific solvents • difficult to assemble under room temperature

early work in the field, is not an ideal material for the MPS-based assessment of cellular responses to drugs,[26] personalized medicine,[27] *in vitro* ADME modeling,[28] and drug discovery.[17] While there is an excellent recent biomaterials book chapter on organ-on-a-chip systems with a brief subsection focusing on alternative materials to PDMS,[3] review articles that specifically feature organ-on-a-chip and MPS work using alternative materials to PDMS are limited.

This article aims to highlight work that strives toward substituting PDMS with alternative materials including elastomers, thermoplastic polymers, glass, silicon, resins, paper, hydrogels, and ceramic materials. A comparison of PDMS to these alternative materials regarding the various potential beneficial material requirements for MPSs and organ-on-a-chip devices, which are typically contingent on the specific application of interest, are highlighted in Table 1. Table 2 provides definitions for the requirements outlined in Table 1. These materials will be discussed in two different contexts: materials to replace PDMS in device fabrication and materials used in PDMS devices to improve cell contact. This review also provides some insight into the direction that PDMS-alternative devices will go in the future as well as what challenges have yet to be overcome in the design of materials to support scalable MPS production.

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PDMS ALTERNATIVES FOR DEVICE FABRICATION

For MPS and organ-on-a-chip device applications where inhibiting absorption, leaching, and autofluorescence or where the capacity for rapid prototyping is of importance, fabricating the bulk of the device with an alternative material to PDMS may be crucial. Alternative materials for this purpose primarily center around the use of elastomers, thermoplastics, glass, silicon, resins, and paper, while advancements in fabrication techniques (3D printing in particular) have led to the utilization of hydrogel-based devices as well. In this section, we describe devices that are essentially PDMS-free and constructed entirely from alternative materials. Since many devices may contain a combination of materials, we have grouped examples below according to the most predominant material in the device that fulfills an important functional role.

Elastomers. Elastomers, typically consisting of entangled polymer chains that make them flexible and stretchable, have been commonly used for organ-on-chip applications.[2,25,29] While PDMS is the most common elastomer used for microfluidic devices, it can absorb small hydrophobic molecules and is incompatible with organic solvents, which may limit its use within specific applications in pharmaceutical research.[17] Substituting PDMS with alternative elastomers without these characteristics is a potential solution. A summary of the properties of alternative elastomers to PDMS including polyester elastomers, tetrafluoroethylene-propylene elastomers, and thermoplastic elastomers, with their advantages and limitations, is illustrated in Table 3.

Polyester elastomers, featuring low-absorption, soft elasticity, and biocompatible properties, are appealing for generating organ-on-chip devices, especially when combined with inert materials such as tissue culture polystyrene (PS). Davenport Huyer et al.[30] described the synthesis and characterization of poly(itaconate-*co*-citrate-*co*-octanediol) (PICO) with tunable soft elasticity. PICO can be easily molded into controllable networks that support cardiomyocyte tissue formation for healthcare applications.[30] Zhao et al.[27] demonstrated the Biowire II platform consisting of elastomeric wires generated from poly(octamethylene maleate (anhydride) citrate) (POMaC) polymer (Figure 1a). The flexible wires within the inert microwells of a microfabricated polystyrene plate allowed for the physical attachment of hydrogel-encapsulated cardiomyocytes to form atrial and ventricular tissues. The long-term stability of POMaC enabled the maturation of cardiac tissues through eight-month electrical stimulation for chamber-specific drug testing and disease modeling of polygenic left ventricular hypertrophy from patient cells.[27] Zhang et al.[33] demonstrated vascularized hepatic and cardiac tissues by engineering the AngioChip device from POMaC, which has since been commercialized by TARA Biosystems. The nanoporosity of the bulk elastomer was tailored using poly(ethylene glycol) dimethyl ether as a porogen that was subsequently leached out. This incorporation of nanopores and microholes in the thin vessel wall of the vascularized construct enhanced the permeability of this system and encouraged angiogenesis during coculture.[33]

Other flexible elastomers such as tetrafluoroethylene-propylene (FEPM), poly(polyol sebacate),[34] and poly(ester amide) elastomers[35] have also been developed for potential application in organ-on-a-chip engineering. A recent study developed FEPM microfluidic devices consisting of two layers of FEPM microchannels with a collagen membrane between

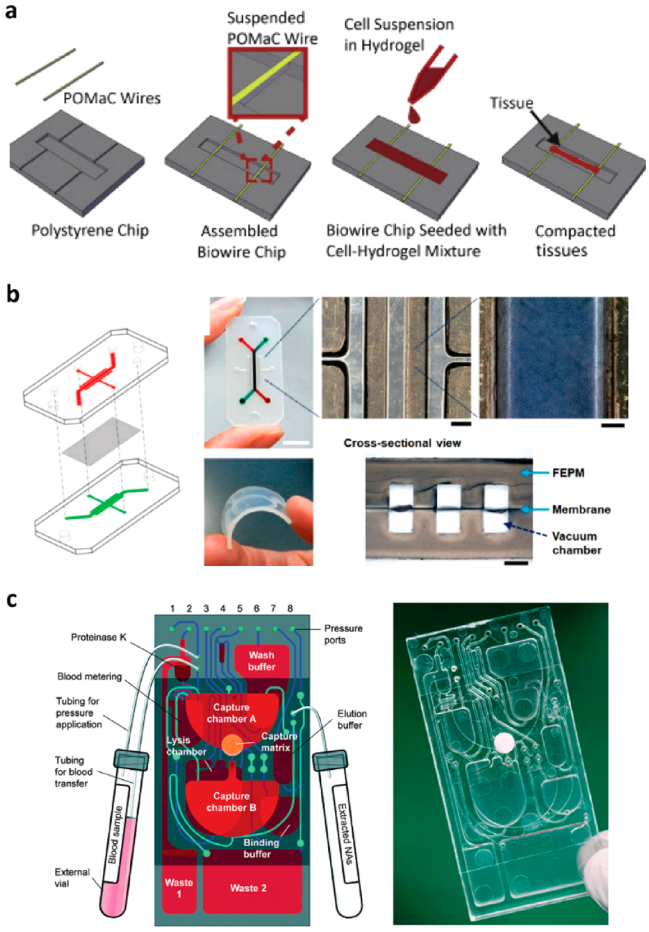

Figure 1. Examples of elastomer-based microfluidic devices. (a) Schematic of a POMaC-based Biowire II platform for generating atrial and ventricular cardiac tissues.[27] Reproduced with permission from ref 27. Copyright 2019 Elsevier. (b) Schematic and optical images of FEPM-based microfluidic device, showing two FEPM channel layers with a collagen vitrigel membrane.[31] Reproduced with permission from ref 31. Copyright 2019 Sano, E.; Mori, C.; Matsuoka, N.; Ozaki, Y.; Yagi, K.; Wada, A.; Tashima, K.; Yamasaki, S.; Tanabe, K.; Yano, K.; Torisawa, Y. (c) Schematic and photograph of an assembled thermoplastic elastomer-based cartridge produced by injection molding and hot embossing.[37] Reproduced with permission from ref 37. Copyright 2019 The Royal Society of Chemistry.

the layers (Figure 1b).[31] This platform can simulate the epithelial−endothelial interface, allowing for both the flow of fluid and the generation of mechanical strain. FEPM was demonstrated to be resistant to the absorption of small hydrophobic drugs, signifying the potential of FEPM platforms for drug discovery. These new elastomers enable the control of mechanical properties as well as, in the case of POMaC, detection of movement through autofluorescence that is generally not possible with PDMS. However, alternative elastomers such as POMaC and FEPM simply minimize, but do not fully eliminate, the small molecule absorption issues, motivating further research into new nonabsorbent elastomers with optical transparency, flexibility, and ease of fabrication.

Advances in polymer engineering over the last 25 years have blurred the lines between traditional elastomers and thermoplastic polymers, and now a wide range of hybrid thermoplastic elastomers with varying degrees of elastomeric properties are used for a plethora of biomedical applications.[36] Thermoplastic elastomers, such as styrene-ethylene-butylene-styrene (SEBS)

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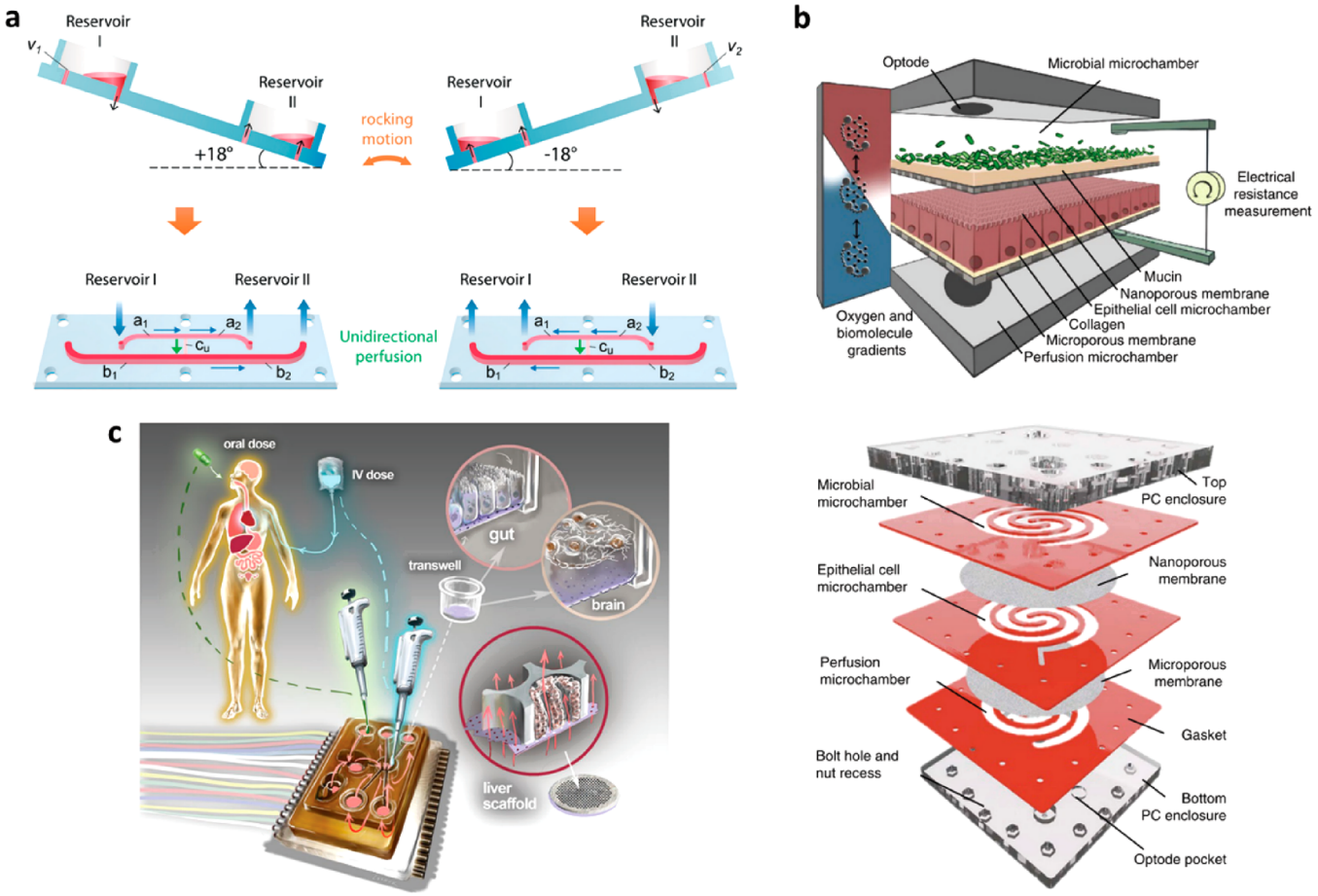

Figure 2. Examples of thermoplastic-based organ-on-a-chip devices and MPSs: (a) Unidirectional flow mechanism of the versatile PMMA/silicon UniChip platform. The cell housing and reservoirs are composed of patterned PMMA, and the silicon perfusion plate is engineered to promote unidirectional flow between two cell-culture reservoirs using a rocking platform that oscillates between +18° and −18° tilting.[63] Reproduced with permission from ref 63. Copyright 2018 The Royal Society of Chemistry. (b) Conceptual schematic of the HuMiX MPS for coculture of gastrointestinal microbiota with human epithelial cells (top). A magnified layout of the structure of the HuMiX system, with elastomeric gaskets with spiral-shaped microchannels between PC enclosures and PC micro- and nanoporous membranes (bottom).[21] Reproduced with permission from ref 21. Copyright 2016 Springer Nature. (c) The concept of the open acrylic/polysulfone/polyurethane human-on-a-chip platform that is an extension of the LiverChip Platform that can house a wide range of cell types using Transwell and specific cell types using more complex, photopatterned 3D structures.[87] Reproduced with permission from ref 87. Copyright 2018 Springer Nature.

block copolymers, have been developed as promising alternatives to PDMS for microfluidic MPSs due to their improved processability, reduced drug absorption, and tunable fluorescence over PDMS while maintaining similar flexibility and elasticity.[1,32] For example, Domansky et al.[32] demonstrated a new fabrication method for SEBS elastomers using injection molding, extrusion, and laser ablation to generate high-throughput microfluidic devices offering fine features and the elasticity required for applications in organ-on-a-chip engineering. The absorption of various model drugs was compared in these systems, where pirfenidone and rhodamine B were shown to absorb 10% and 21% less with SEBS than PDMS, while coumarin absorbed 5% more. These results show that SEBS can reduce the absorption of some drug compounds as compared to PDMS, which offers potential for their use in biological applications including drug screening with organ-on-a-chip devices.[32] Brassard et al.[37] demonstrated a centrifugal on-chip platform fabricated by hot embossing and injection molding with a thermoplastic elastomer (Figure 1c). The microfluidic chip was attached to a standard laboratory centrifuge with pneumatic actuation, allowing the extraction of nucleic acid from whole blood with an output comparable to some of the best commercial kits. Domansky et al.[38] compared polyurethane-glass and PDMS-glass hybrid microfluidic devices. Here, the polyurethane-glass devices experienced significantly less small molecule (rhodamine B) absorption with similar human umbilical vein endothelial cell (hUVEC) viability to PDMS hybrid devices after being coated with fibronectin. Lind et al.[39] demonstrated a multimaterial 3D printing technique to produce cardiac MPSs with integrated gauge wires. The wires were fabricated from a thermoplastic polyurethane ink filled with conductive nanoparticles, which was used to measure the force generated by cardiac tissues. Compared to PDMS, thermoplastic elastomers can be fabricated by industrial technologies such as injection molding in a high-throughput manner and can possibly be used in advanced fabrication techniques such as additive manufacturing.

Thermoplastics. Thermoplastic polymers are promising PDMS-alternative materials for the fabrication of organ-on-a-chip devices and MPSs as they are generally rather inexpensive, less prone to monomer leaching, biocompatible, and have good mechanical strength, but are relatively inflexible.[40] The processability and mechanical strength of thermoplastics for

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3D macroscale tissue engineering scaffolds translate into precise, potentially high-throughput, structures for culturing tissues on organ-on-a-chip systems and MPSs. However, the biodegradability of thermoplastics used for macroscale systems, such as poly(lactic acid) (PLA)[41−44] and polyhydroxyalkanoates,[45] can lead to variability and are less desired for microscale structures, resulting in thermoplastic-based MPSs instead being typically composed of polyacrylates, polysulfones, polycarbonates, cyclic olefins (co)polymers, and combinations thereof. A comparison of the properties of these thermoplastic materials are shown in Table 4.

Stemming from their mechanical characteristics, transparency, and lack of small molecule absorption, several acrylics, including polystyrene (PS) and poly(methyl methacrylate) (PMMA), have been used for organ-on-a-chip devices and MPSs.[27,33,46−50] Commercially produced acrylic sheets can be micromilled to fabricate structures for devices or highly stable acrylic master molds with a wide range of potential surface features and topologies for hot embossing of other thermoplastics in a high-throughput, rapid prototyping manner.[51−55] One example combined high-throughput computer numerical control (CNC) micromilling and solvent bonding techniques to fabricate a three-layered open-microfluidics PMMA device that mimics the lung microenvironment.[46] The benefits of impermeability to small molecules of micromilled PMMA devices was highlighted in a study by Nguyen et al.[26] where lung adenocarcinoma cells were cultured on a polyethylene terephthalate (PET) membrane sandwiched between either micromilled PMMA or patterned PDMS microfluidic channels in analogous MPSs. The PMMA devices showed a significant, reliable cytoxicity to the drug vincristine, while the PDMS devices did not, due to drug absorption by PDMS.[26] Similar differing cellular responses to the antidepressant drug fluoxetine were also observed between analogous PDMS and PS in the culture of human embryonic kidney (HEK) cells, where the effectiveness of fluoxetine was decreased in the PDMS devices due to drug absorption.[56]

A rigid, transparent, 3D-printable photo-cross-linkable polymer that simulates PMMA, Veroclear, has proven useful as 3D printed structures for MPSs.[57,58] 3D printed Veroclear microfluidic channels were developed within a chip for the coculture of primary hepatocytes and nonparenchymal cells over 14 days under gravity-mediated bidirectional fluidic flow.[59] The shear stresses put forth by the bidirectional flow resulted in more mature hepatic cells that synthesized greater amounts of albumin and urea in comparison to static cultures and produced interleukin-8 (IL-8) in response to bacterial lipoprotein challenges.[59] This was adapted into a completely modular body-on-a-chip device containing several organ chambers manufactured with 3D-printed Veroclear polymer, separated by polycarbonate membranes, with physiologically relevant, unidirectional flow through each organ chamber controlled by tilting the system.[60] A series of Veroclear-based, gravity-driven flow systems (with polycarbonate membranes) were developed based off this work, from blood−brain barrier models[61] to escalating degrees of multiorgan MPSs (from 2 to 13 organ compartments).[60,62] This work culminated in the versatile UniChip (Figure 2a), which is comprised of PMMA sheets developed via high-throughput laser ablation and solvent bonding supporting a silicone perfusion channel that had gravity-driven, unidirectional flow.[63] The UniChip could prove useful for organ-on-a-chip culture of a wide range of shear-stress sensitive tissues, and the 3D printing of Veroclear could allow for prototypes to be developed in a more rapid manner than PDMS, which typically relies on soft photolithographic techniques.

Rapid prototyping using the CNC micromilling technique described for PMMA can be applied to other thermoplastics, such as polystyrene and polycarbonate.[64] Polycarbonate (PC) is a hard material that many devices use as a tissue-bearing porous membrane component.[62,65,66] Few MPSs are primarily composed of PC, some of which are rationalized as inexpensive alternatives to other devices that could be more accessible for widespread use.[67,68] A particularly interesting PC-based system that exploits the lack of oxygen permeability of PC is the HuMiX (human-microbial crosstalk) model, initially reported by Shah et al.[21] (Figure 2b). This is a modular microfluidics human-microbial coculture model developed by sandwiching two micromilled polycarbonate microfluidic channel enclosures between silicone rubber gaskets. Polycarbonate is gas impermeable, so the oxygen concentration can be precisely controlled, allowing for coculture of Caco-2 cells and the facultative anaerobe *Lactobacillus rhamnosus* GG (LGG) and/or the obligate anaerobe *Bacteroides caccae*. Molecular analyses of the effects of coculture were performed on all cell types involved, demonstrating that the transcriptional responses from human epithelial cells cocultured with LGG and *Bacteroides caccae* using the HuMiX system were consistent with *in vivo* data.[21] HuMiX was later used to investigate the effects of synbiotics on cocultured colorectal cancer cells[69] and could elucidate the uncertainties of the host-microbe interactions in the gastrointestinal tract.[70] An additional PC-based platform that models the human cornea was developed to assess the influence of a commonly used permeation enhancer in improving the diffusion of a model drug (that would otherwise be absorbed in a PDMS-based system) into the anterior eye.[71,72]

Cyclic olefin homopolymers and copolymers (COPs/COCs) have extremely low impurities as well as the beneficial properties of other thermoplastics.[73,74] One coculture system showed the biotransformation, toxicity, and codrug treatment of aflatoxin B1 and benzoalphapyrene on an interconnected liver and kidney within a COC-based microfluidic chip.[75] Another platform, EVIDENT (ex vivo immune-oncology dynamic environment for tumor biopsies), is a scalable COC-based MPS that is capable of sustaining up to 12 tumor fragments that interact with circulating tumor-infiltrating lymphocytes (TILs) for several days to study TIL infiltration and tumor apoptosis.[76] Being fabricated from optically clear COC, quantification of temporal levels of TIL infiltration and cell death can be performed in real time, and the EVIDENT system effectively mimicked *in vivo* responses of tumorous tissues to anti-PD-1 immune checkpoint inhibitor treatments.[76]

To date, there are few examples of organ-on-a-chip devices and MPSs solely made of other thermoplastics, such as polysulfone, PLA,[77] and PET (which is often used as a porous tissue supporting membrane),[78−80] but these materials could attain greater utilization as the MPS field expands. There are, however, several composite MPSs that have been developed that take advantage of the beneficial properties of multiple thermoplastic PDMS-alternative materials, which can be vital for studies in which the absorption of small molecules would be detrimental.[78−81] Organ-on-a-chip devices and MPSs that aim to model *in vivo* human drug metabolism, metabolomics, and PK/PD, which, if proven effective enough, could

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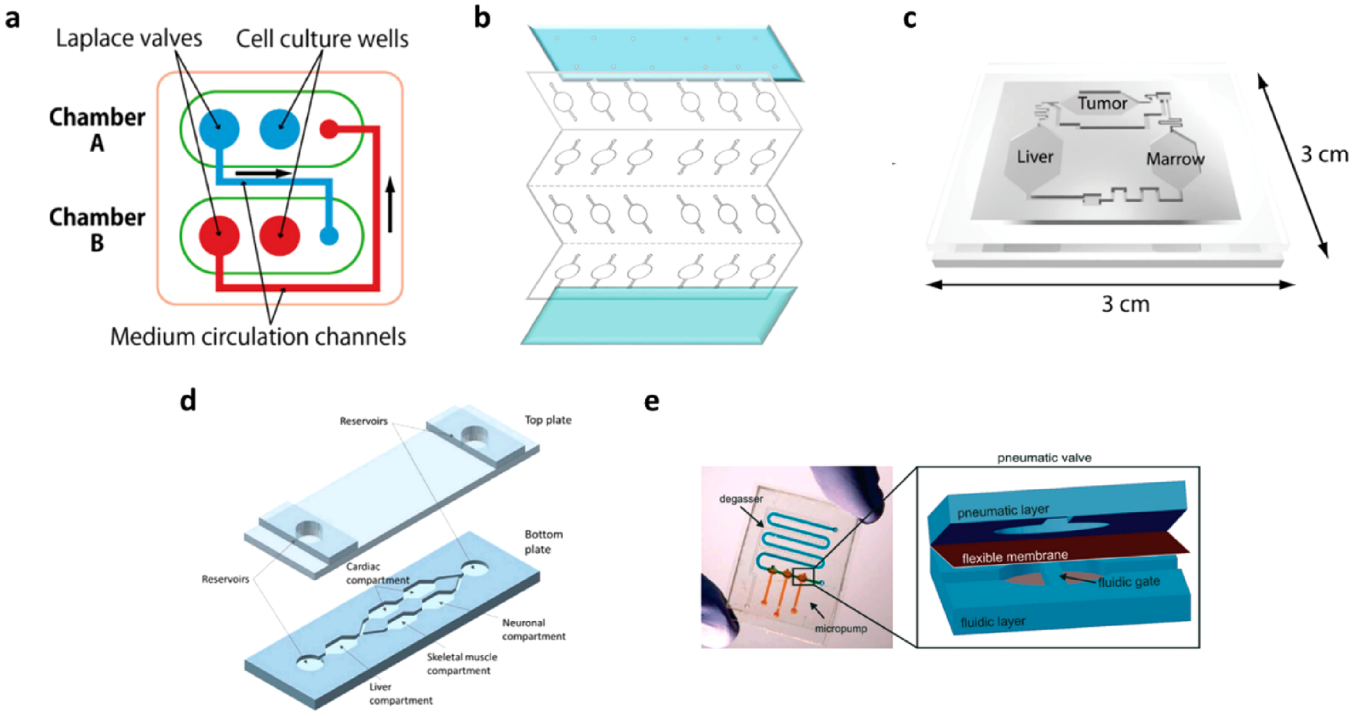

Figure 3. Examples of glass-, adhesive-, and silicon-based organ-on-a-chip devices and MPSs. (a) Schematic representing a culture unit of a glass-based organ-on-chip device.[102] The overall device is fully fabricated of glass and contains eight culture units. Reproduced with permission from ref 102. Copyright 2018 The Society for Biotechnology, Japan. (b) Magnified view of glass-, adhesive-, and PMMA-based six organoid MPS.[108] The culture chambers and channels are made of layered adhesive film, enclosed on one side by a glass slide and on the other by a PMMA lid. Reproduced with permission from ref 108. Copyright 2020 Acta Materialia Inc. (c) Schematic of the first iteration of a silicon-based MPS,[115] reproduced with permission from ref 115. Copyright 2009 The Royal Society of Chemistry. (d) Schematic of a later iteration of a silicon-based MPS from the same group.[28] The first iteration utilized a pump to provide flow; however, the later model allows for pumpless recirculating flow. Reproduced with permission from ref 28. Copyright 2016 Springer Nature. (e) Optical image and schematic of membrane-integrated, ostemer-based organ-on-chip device.[119] The membranes are polycarbonate, and device layers are fabricated of ostemer. The degasser is the only component containing PDMS. Reproduced with permission from ref 119. Copyright 2015 The Royal Society of Chemistry.

ultimately replace standard in vitro and animal drug testing work, require the entire device to comprise materials that do not significantly absorb the drug of interest and adversely affect these studies. A particularly indicative example of this is the LiverChip platform, a modular MPS platform that can incorporate many different cell types in on system that CN Bio Innovations has commercialized.[82−89] The LiverChip platform was initially an open platform made from micro-machined and solvent bonded polystyrene and polycarbonate (later acrylics and polysulfone) with bovine serum albumin (BSA)-coated polyvinylidene fluoride-based hepatocyte-supporting filters and a polyurethane elastomer tubing system to pump media throughout the device—all materials that limit drug absorption.[82] This platform was used to determine oxygen consumption rates,[82] to demonstrate that a 3D culture of hepatocytes promotes their stable expression of metabolism-related biomarkers,[83] and for a pharmacokinetic analysis of hydrocortisone.[84] The basis of these acrylic−polysulfone−polyurethane systems was developed into a human-on-a-chip device (Figure 2c), an interconnected body-on-a-chip platform capable of housing up to 10 different 3D cultured tissues in one network with an integrated mixing system[87] that was used to examine drug pharmacokinetics,[86] crosstalk between tissues,[85] and assess inflammation by short chain fatty acids in an ulcerative colitis model.[89] A recent study assessed the influence of 12 metabolites of the drug tolcapone on brain tissues via introducing tolcapone into human-on-a-chip device with seven integrated organ tissues, observing that 18 key biomarkers of human brain cells were significantly altered.[88] These studies highlight the potential impact of organ-on-a-chip platforms and MPSs that can further recapitulate *in vivo* drug metabolism, metabolomics, and PK/PD.

The lack of permeability of thermoplastics to potential APIs leads to thermoplastic materials only being susceptible to surface adsorption rather than potential adsorption and absorption in PDMS constructs.[90] This difference alone could lead to significant alterations in API concentrations throughout the course of a study. For example, in a simplified adsorption/absorption study, several cardiac drugs were placed in either PDMS or polystyrene (PS) tissue culture wells, and the concentration of drug retained within the solution was assessed over 3 h.[11] Over this short time frame, verapamil and nifedipine were absorbed 20−50% more in PDMS versus PS wells, and >80% of bepridil was absorbed by PDMS, while just under 50% of this hydrophobic calcium channel blocker was adsorbed by PS. A more thorough and MPS-relevant study was performed by van Midwoud et al.,[91] where the adsorption of small molecules (7-ethoxycoumarin and testosterone and their metabolites) within simple microfluidic tissue culture model chips made from PDMS, PMMA, PS, PC, and COC was assessed. PMMA and PDMS chips adsorbed around 20% of 7-ethoxycoumarin that was introduced to the devices, while PC, PS, and COC had no adsorption. PDMS was also found to adsorb 15% of testosterone and 5−15% of most of its metabolites, while PMMA adsorbed 10−15% of the more hydrophobic testosterone, and again PC, PS, and COC had no

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Table 4. Properties of Thermoplastic Materials That Have Been Used for the Bulk of Organ-on-a-Chip Devices and MPSs

thermoplastic	T_g [°C]	T_m [°C]	water absorption [%]	optical clarity	UV transparency	oxygen permeability [cm^3.mm/(m^2.day.atm)]	advantages	disadvantages	ref
poly(methyl methacrylate) (PMMA)	100−122	250−260	0.3−0.6	excellent	>340 nm	5.8	• inexpensive • rigid • ease of fabrication/modification (hot press-microwave, solvent, thermal bonding) • less hydrophobic	• injection molding/hot embossing (expensive equipment)	46, 92−94
polycarbonate (PC)	145−148	260−270	0.12−0.34	excellent	>360 nm	91−124	• durable • inexpensive • good machining properties	• absorbance in UV • high temperature of thermal bonding (may alter channel geometry)	92, 93, 95
cyclic olefin (co) polymer (COC/COP)	70−155	190−320	0.01	excellent	>250 nm	>118−157	• low water absorption • high UV transmittance • low autofluorescence • excellent dimensional stability • ease of fabrication/modification (solvent, thermal bonding)	• highly hydrophobic (may need surface treatment to minimize adsorption of analytes) • expensive to mold	91, 92, 96−98
polystyrene (PS)	92−100	240−260	0.02−0.15	excellent	>300 nm	118−157	• bioinert • rigid • inexpensive • ease of fabrication/modification (solvent, thermal bonding)	• injection molding/hot embossing (expensive equipment) • difficult to thermally bond • autofluorescent postheat treatment	92, 93, 98, 99
polysulfone	170−187	180−190	0.3−0.4	fair	N/A	91	• less hydrophilic • minimal surface adsorption and bulk absorption of hydrophobic moieties • high toughness, stability	• not optically clear • expensive to develop	86, 92, 93
polylactic acid (PLA)	60−65	130−180	1−6	excellent	>300 nm	200 (film), limiting factor in PLA device (2.5×10^{-12} m^2/s)	• environmentally friendly • inexpensive • easily workable for rapid prototyping • no autofluorescence	• hydrolytically degradable • must be chemically modified to be suitable for cell culture	77, 92, 93

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adsorption.[91] While studies such as this (using relatively generic MPS designs) are important in gauging comparisons between organ-on-a-chip and MPS device material characteristics, the degree of absorption is highly specific to the conditions of the study of interest, such as the properties of the molecule of interest (size, hydrophobicity), the materials used for the device fabrication, the device design (channel dimensions, lengths), whether the device has been surface modified (and what it is modified with), the time frame of the experiment, the fluid velocity, etc.[17] Regardless, there appears to be an opportunity to quantify the absorption and adsorption of multiple potential drugs/hydrophobic small molecules to generally compare potential adsorption on MPSs made from differing materials in a more comprehensive manner.

Glass. Glass-based microfluidics have been used since the early days of the field, so glass micron-scale fabrication processes are well established.[100,101] Glass organ-on-a-chip devices and MPSs are now being developed as an alternative to PDMS due to their low drug absorptivity.[100,102−105] Similar to PDMS, glass devices are biocompatible and optically clear. Glass is also easily surface-modified, and cells readily adhere to plain or modified glass. However, glass microfluidic devices are expensive (near $500 USD to fabricate by one estimate[106] or 10 times higher than PDMS by another estimate[102]), though there are efforts to make such devices in a more rapid and cost-effective manner.[106]

In organ-on-a-chip devices and MPSs, glass is used either alone or with other components, such as thermoplastics or adhesives. Notably, a fully glass-based organ-on-a-chip device has been reported by Hirama et al.,[102] including comparisons to an analogous PDMS device (Figure 3a). The authors used a variety of techniques to fabricate a device made of two thermally bonded glass layers, including microvalves and channels. Wet-etching combined with sandblasting was used to create deep channels, CNC machining was used to engrave cell culture wells into a glass plate, and wet-etching alone was used to form valves on a second glass plate. Cells were immediately adherent to glass devices, and fluorescent staining for fatty acids in HepG2 cells indicated less background absorption of fluorophore in glass devices as compared to PDMS devices.[102] In terms of device features, microvalves in glass-based devices exhibited more consistent flow behavior than those in PDMS devices, though glass devices resulted in more air bubbles and higher cost. This increased incidence of air bubbles is due to the gas-impermeability of glass, which is often a disadvantage in using glass-based organ-on-chip devices. During temperature changes such as placement into the incubator, the solubility of dissolved gases is lowered and results in bubble accumulation as gases cannot diffuse through device walls. An earlier, all-glass device was reported for use in pancreatic islet culture.[104] This platform allowed measurement of oxygen consumption, and online fluorometric metabolite measurement. Here, the gas-impermeability of glass was found to be an advantage, allowing accurate measurement of oxygen consumption as no gas can diffuse into the platform through the channel walls. The gas-impermeability of such devices may also be an advantage in cultures requiring anaerobic conditions.[107]

In order to address some difficulties in device design using glass, such as cost and fabrication difficulty, Rajan et al.[108] used an integrated, multiorganoid microfluidic MPS platform based on glass, PMMA, and an adhesive, and proved its utility in drug testing (Figure 3b). This device was used to culture up to six linked organoids and demonstrated liver metabolism of prodrugs resulting in toxic effects on downstream organoids. The organoids were viable for up to 28 days and exhibited functional biomarkers over long-term culture. These MPSs, unlike other glass-based systems, were low-cost due to the combination of glass and other, cheaper materials.

Another organ-on-a-chip system, OrganoPlate, which has been commercialized by MIMETAS, is a microfluidics-based system in a multiwell format developed from glass and polymer and a cell-supporting hydrogel that has various configurations that can be used to build various different organ models.[109] The role of hydrogels on these glass plates is mainly to facilitate tissue fabrication, by either providing structural support for cells[110,111] or encapsulating cells to mimic the *in vivo* microenvironment.[109,112] A variety of models have been established by different groups, including kidney,[111,113] gut,[110] pancreatic cancer,[109] brain,[112] and microvessels.[114] A major advantage of OrganoPlate in organ-on-a-chip applications is its ability for high-throughput analysis, yet the shortcomings are the noncircular channels and perhaps the lack of structural or topographical complexity that might be necessary for certain tissues, which are limitations with glass-based systems. It is possible that commercialization of this device was enabled through the use of multiple materials to reduce the cost of fabrication in comparison to full-glass chips. This trend of including alternate materials allows the bulk of a device to be built out of inexpensive, easy-to-fabricate resins or tissue culture plastics, while critical cell-contacting components may be fabricated from more expensive glass or silicon.

Silicon. Silicon-based devices have also been used and have many of the same benefits as glass.[28,106,115] Silicon, however, is not optically clear, and thus a portion of the device must be nonsilicon for *in situ* imaging. Additionally, silicon has been widely used in the fabrication of electronics, and techniques for fabricating silicon-based platforms, including dry or wet etching, laser-drilling, sand-blasting, and direct, anodic, or adhesive bonding, are well established.[100] Silicon-glass microfluidic devices have been reported that are disposable, inexpensive (close to $5 USD), and can be rapidly fabricated for high-throughput experiments to address the main disadvantages of glass;[106] however, such combined silicon-glass devices have yet to be widely utilized within MPS applications.

A notable example of silicon-based MPSs demonstrated metabolism-dependent cytotoxicity of cancer drugs using a microcell culture analogue (μCCA) microfabricated using a silicon wafer (Figure 3c).[115] The μCCA included liver, tumor, and bone marrow chambers. Cells could be cultivated in hydrogels with pump-driven flow of cell culture media. This technology was further developed into a five-compartment MPS with gravity-driven flow for drug ADME studies (Figure 3d).[28] The fabrication using silicon allowed this system to include functional readouts for four tissues: albumin and urea production in liver compartment; contractility using microcantilevers in the cardiac compartment; electrophysiological recordings in the neural compartments; and muscle contractility in the skeletal muscle compartment. The authors reported functional and viable tissue in all compartments after 2 weeks of coculture. It was demonstrated that this four-organ system mimicked human response to five different drugs during 14-day toxicological studies.[28]

Adhesives or Epoxy Resins. Though sometimes used as a component in glass or silicon devices, adhesives such as epoxy

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or medical-grade glues have been used as the sole material in organ-on-chip engineering. Devices have been fabricated with unique materials as well as more common materials such as SU-8[116] and NOA-81.[117,118] A unique nonglass device based on a thiol-ene epoxy adhesive, termed *ostemer*, has also been reported by Sticker et al.[119] (Figure 3e). Here, the formation of various features including microvalves and microfluidic pumps was demonstrated in *ostemer*-based devices. They fabricated multilayer and membrane-integrated MPSs with vascular interfaces. Higher human umbilical vein endothelial cell (hUVEC) and fibroblast viability was demonstrated in *ostemer* as compared to polystyrene. It was additionally demonstrated that cells were adhering to *ostemer*, and osteogenic differentiation of adipose-derived mesenchymal stem cells was supported in the *ostemer*-based platform.[119] Further, *ostemer*-based devices had low water vapor permeability and were likely to be bubble-free as compared to PDMS devices. Finally, *ostemer* exhibits blue autofluorescence, but fluorescent analysis was not significantly affected.

Devices have also often been developed using SU-8, such as that of Ayuso et al., which was developed to study chemotaxis in a 3D environment over short- or long-term culture (24 h or 7 days, respectively).[116] The design allowed for a confined hydrogel between two microchannels delineated by SU-8 microposts. The hydrophilic nature of SU-8 combined with square-shaped posts led to robust interface halting of flow; this prevented filling and blockage of microchannels by hydrogel during gel casting and enabled hydrogel confinement simply by applying a droplet to the inlet of the chip. PDMS-based devices are often rendered hydrophilic in order to enable such filling; this represents an advantage of SU-8 over PDMS for MPS systems. Another common adhesive used in designing MPSs is NOA-81, which Li et al. utilized for the culture of SH-SY5Y in a device made entirely of NOA-81.[117,118] Devices made with this glue were shown to be biocompatible, supporting cell adhesion and proliferation for over 1 week and higher viability in NOA-81 as compared to PDMS.

Paper-Based Devices. Paper-based MPSs are sustainable, naturally derived materials, albeit they are utilized less often than the previously discussed PDMS-alternative materials. Paper-based systems have several advantages such as accessibility, low-cost, high porosity, flexibility, ease of sterilization, ease of chemical or biological modifications, similarity to native extracellular matrix (ECM), ease of manipulation, and biocompatibility.[120,121] Multiple layers of paper can be stacked in order to study various layers of a 3D culture (Figure 4).[122] Despite paper's advantages in many aspects, it has several pitfalls. Common issues with paper-based systems are loss of mechanical strength in the wet state and limitations on thickness to achieve transparency.[123] These systems have been shown to effectively model hypoxia in cancerous tissues,[124] ischemia in cardiac tissue,[125] and bone tissue.[126]

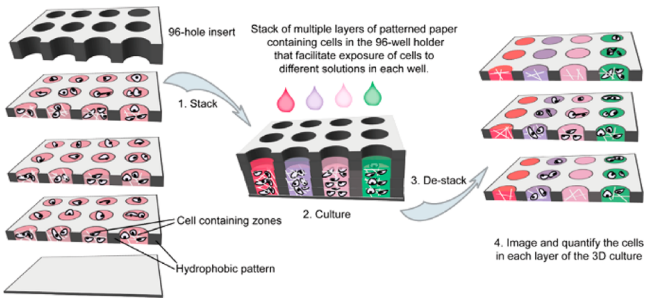

Figure 4. Schematic of a paper-based PDMS-alternative organ-on-a-chip MPS platform containing multiple layers of paper, each seeded with mammalian cells.[122] Reproduced with permission from ref 122. Copyright 2013 American Chemical Society.

Hydrogels. Hydrogels themselves are less frequently used as the primary device fabrication material because the high compliance of hydrogels presents a major challenge to maintaining the mechanical integrity of a device and could possibly limit their long-term use. As such, supplementary materials are often needed to provide structural support or act as a mold during the device fabrication process.[127] Since many organ-on-a-chip and MPS applications incorporate microchannels or hollow tubes to mimic vasculature, the development of luminal structures within hydrogels (which is likely to be monolithic) needs to be addressed before hydrogels can be used as the fabrication material for organ-on-a-chip devices. Another issue is that hydrogels are not robust to all the common sterilization methods and therefore may necessitate a sterile environment during fabrication as opposed to sterilization postfabrication and before use. Despite the challenges associated with using hydrogels as a primary fabrication material, organ-on-a-chip devices comprised of hydrogels offer several desirable properties. The first and foremost is the biocompatibility of hydrogels, which can provide cells with a supportive microenvironment that closely mimics the *in vivo* ECM. Hydrogel-based devices provide a 3D matrix with greater similarity to native tissues compared to the 2D or 2.5D structure reconstituted in some of the simpler designs. Furthermore, the use of cell-laden hydrogels with tubular structures makes it possible to construct 3D parenchymal tissue with a vascular network. Lastly, the elasticity of hydrogels enables specific physiological activities, such as breathing, to be modeled in the studies.

To fabricate a monolithic hydrogel with a vascular network embedded inside, stereolithographic printing has been one of the commonly used approaches for organ-on-a-chip applications. Stereolithography is a technique that creates 3D constructs by light-induced solidification of a prepolymer solution layer-by-layer, often by radical photopolymerization.[128] The use of stereolithography for in vitro models is promising due to its potential for 3D free-form printing at a high spatial resolution, which makes it possible to reconstitute complex *in vivo* structures.[128] The choice of photoabsorbers is important with regard to creating a hollow perfusable vasculature in a hydrogel without the narrow void spaces being clogged by inadvertent polymerization, as it dictates the light penetration depth into the prepolymer solution (Z resolution) and confines the polymerization to the defined layer thickness.[128,129] Recently, the development of stereolithography enabled researchers to generate mechanically stable, self-contained, dense, 3D perfusable chip systems using a poly(ethylene glycol) diacrylate (PEGDA) hydrogel.[128,129] Grigoryan et al.[129] selected tartrazine as the photoabsorber for its low toxicity and minimal residue after washing. They utilized stereolithographic 3D printing to fabricate a 3D, functional PEGDA bicuspid venous valve as well as an alveolar model with a highly branched vascular network in which the oxygenation and flow of human red blood cells during tidal ventilation and distension was explored (Figure 5a). Zhang et al.[128] built a 3D chip with confined culture volumes traversed and surrounded by perfusable

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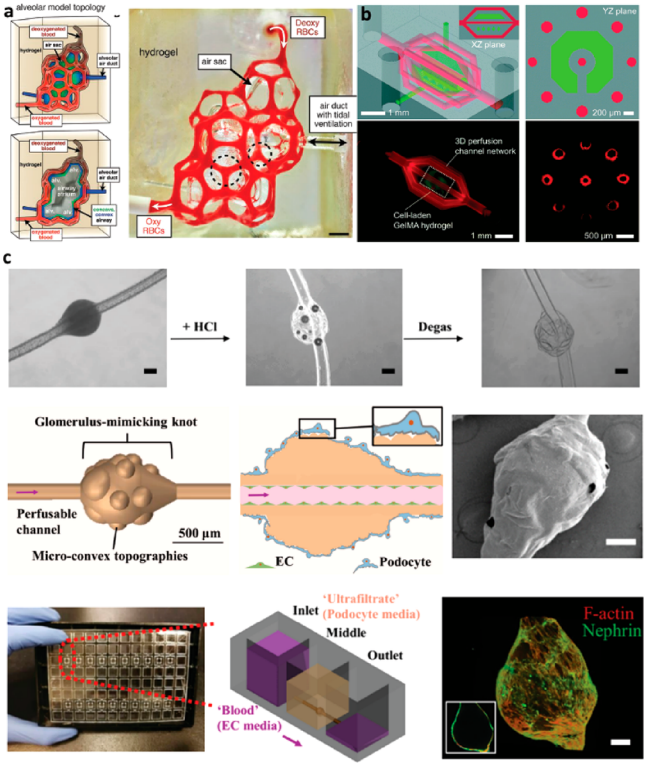

Figure 5. Examples of hydrogels as a primary device fabrication material: (a) An alveolar model designed with highly branched vasculature created by 3D printing a PEGDA hydrogel. Left: design of an alveolar model topology with an ensheathing vasculature (top) and cutaway view (bottom) of the model alveoli with a shared airway atrium (convex: blue, concave: green). Right: Photograph of a printed hydrogel while red blood cells (RBCs) were perfused and the air sac was ventilated with O_2 (scale bar: 1 mm).[129] Reproduced with permission from ref 129. Copyright 2019 Bagrat Grigoryan, Samantha J. Paulsen, Daniel C. Corbett, Daniel W. Sazer, Chelsea L. Fortin, Alexander J. Zaita, Paul T. Greenfield, Nicholas J. Calafat, John P. Gounley, Anderson H. Ta, Fredrik Johansson, Amanda Randles, Jessica E. Rosenkrantz, Jesse D. Louis-Rosenberg, Peter A. Galie, Kelly R. Stevens, Jordan S. Miller. (b) 3D perfusable PEGDA hydrogel chip fabricated using a stereolithographic 3D printing technique. Top: chip design viewed from different angles where the culture chamber is surrounded by eight perfusable vascular channels and traversed by a central one. Bottom: fluorescence micrograph (left: top view, right: cross-sectional view) of the tissue construct with the vascular channels coated by rhodamine (red) and the chamber filled with fibroblast-laden (calcein AM, green) gelatin hydrogel.[128] Reproduced with permission from ref 128. Copyright 2017 The Royal Society of Chemistry. (c) Biomimetic glomerulus filtration barrier on a 96-well plate platform. Top: fabrication of an alginate fiber that has a knot with microconvex topography (scale bar: 200 μm). Middle: left: design of the structure of the alginate fiber with a glomerulus mimicking knot; middle: perfusable glomerulus model with endothelial cells seeded in the lumen and podocytes seeded on the knot; right: SEM image of the microconvex topography on the scaffold surface (scale bar: 200 μm). Bottom: left: assembly of the alginate fibers onto a 96-well plate; middle: gravity-driven perfusion through a fiber in a three-well configuration; right: confocal microscopy image of podocytes on the knot stained with F-actin (red) and nephrin (green), with the inset showing a longitudinal cross-section (scale bar: 100 μm).[134] Adapted with permission from ref 134. Copyright 2020 American Chemical Society.

vascular-like networks (Figure 5b). They selected a medium molecular weight PEGDA to balance the mechanical stability and the diffusivity of the hydrogel construct, and demonstrated continuous perfusion culture of fibroblasts for a week, observing higher cell viability compared to the counterparts cultured in a static condition.[128] This 3D perfusable chip system has the potential to be scaled up and to culture multiple cell types fluidically connected by the spatially controlled vascular networks within a single chip device, which can serve as a model for studying systemic drug effects.

Besides stereolithographic printing, sacrificial molding with 3D printed templates, often combined with 3D bioprinting, can form hollow perfusable tubular structure within a hydrogel that resemble vasculature *in vivo*. Instead of directly printing the hollow structure, a sacrificial template is first printed, encapsulated within a hydrogel, and later removed to leave hollow voids inside the hydrogel. The geometry of the hollow structure within the hydrogel can be controlled through the design of the sacrificial template. Early in 2012, Miller et al.[130] used 3D filament networks of carbohydrate glass as a sacrificial template to construct solely hydrogel 3D engineered tissues with perfusable vascular networks. In this study, the sacrificial template was cytocompatible and dissolvable in media so that living cells could be encapsulated in the ECM-based hydrogel upon casting. More recently, Ji et al.[131] developed a novel bioprinting approach in which sacrificial ink could be embedded into the photocurable hydrogel (methacrylated alginate or methacrylated hyaluronic acid) during the layer-by-layer printing and later removed by immersing in PBS to create perfusable channels.

The 3D bioprinting techniques can also be applied to fabricate hydrogel-based devices without the use of a sacrificial mold if a luminal structure is not required for an organ-on-a-chip application. The 3D bioprinting approach enables 3D patterning of multiple cell types in a configuration with high mimicry of the native organs. For instance, Lee et al.[132] designed a one-step fabrication method of organ-on-a-chip using 3D bioprinting, which allowed heterotypic cell types and ECM-based hydrogels to be positioned in a predefined biomimetic manner. They demonstrated the application of this technique in the context of a liver-on-a-chip where hepatocytes and endothelial cells were cocultured under continuous flow. Ma et al.[133] developed a hepatic model composed of a triculture of human induced pluripotent stem cell (hiPSC)-derived hepatic progenitor cells (hiPSC-HPCs) and supporting endothelial and mesenchymal cells. They used a customized digital light processing-based 3D printing system, through which the biomimetic liver lobule patterns were transferred to the tissue construct composed of cell-loaded gelatin methacrylate and glycidal methacrylate-hyaluronic acid. This triculture model was shown to enhance liver-specific gene expression and functions of the hiPSC-HPCs.

Hydrogels can also be used in complex structures and topographies to better mimic the natural extracellular environment. Here we highlight a recent study by Xie et al.[134] that demonstrated a unique methodology termed "microfluidic spinning" to develop hydrogels with specific topography and integrate them onto a well plate platform where the structure and topography of hydrogels played an important role in mimicking the native tissue (Figure 5c). They extruded hollow alginate fibers with a perfusable channel and a knot with microconvex topography, which could reconstitute the glomerular filtration barrier after they were assembled in a bidirectionally perfused three-well configuration via gravity-driven flow. The perfusable channel lined with endothelial cells

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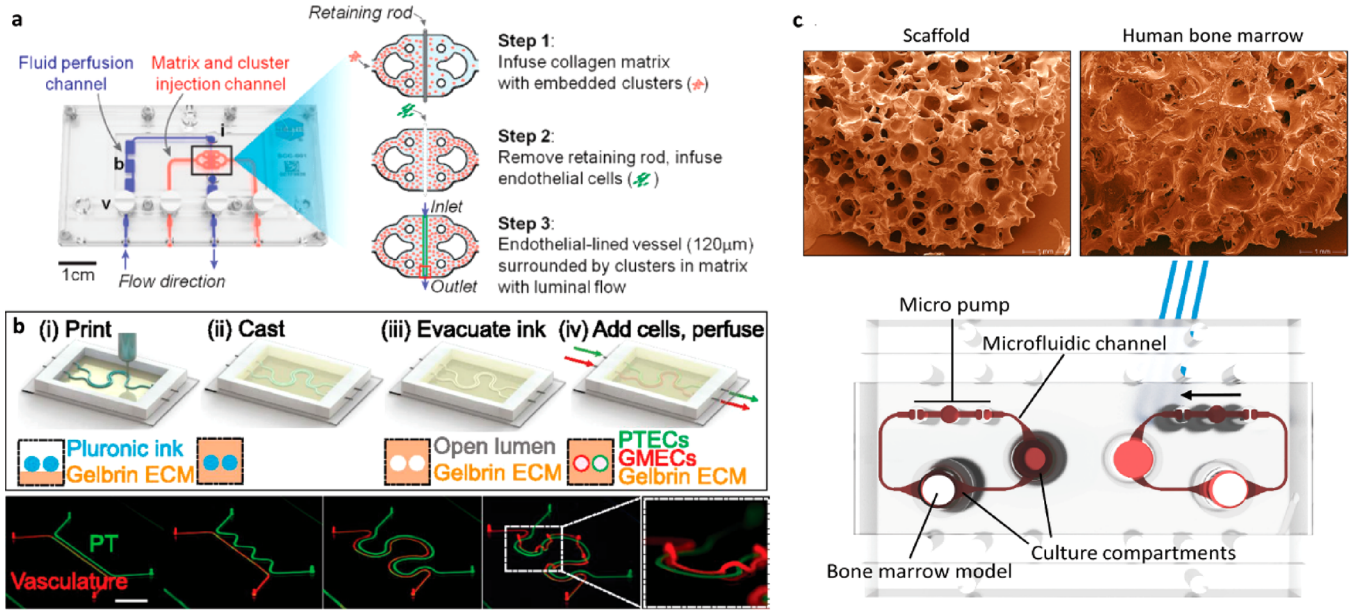

Figure 6. Examples of cell-contacting materials in organ-on-a-chip devices: (a) 3D cancer-on-a-chip constructed using Nortis single-channel MPS. Steps in seeding the device are shown. The device contains ports for extracellular matrix collagen (red) and luminal flow (blue). (b: bubble trap; i: injection port; v: valve.)[139] Reproduced from ref 139. with permission from Elsevier. (b) 3D bioprinted vascularized hydrogel proximal tubule within a silicone supporting structure. Top: schematic view of the fabrication process. Bottom: design and fabrication of simple and complex proximal tubule models (scale bar: 10 mm).[127] (c) SEM comparison of ceramic-based scaffold to human bone marrow (top). This scaffold was placed in a PDMS based device for the culture of hematopoietic stem and progenitor cells (HSPCs) (bottom).[142] Reproduced from ref 142. with permission from John Wiley & Sons.

simulated the vascular side of the glomerular filtration barrier, whereas the topographic knot which was situated in the middle well and covered by podocytes mimicked the other side of the barrier. Both the knots and their topographic surface were shown to contribute to the formation of a functional barrier.[134] This research exemplifies how hydrogels are uniquely suited to be controllably constructed into complex topologies that can be employed to fabricate advanced cell-supporting structures that can be utilized to better mimic and recapitulate specific tissues.

ALTERNATIVE CELL CONTACTING MATERIALS IN PDMS-BASED DEVICES

As several of the previous examples reveal, many devices utilize combinations of materials to take advantage of the benefits of their composite materials within a single system. There are many cases where these alternative materials are used within organ-on-a-chip devices and MPSs as the cell contacting material to improve cell adhesion, utilize more consistent and structurally sound cell contacting membranes, and better mimic the cellular microenvironment for specific types of cells. These cell interfacing materials are often hydrogel-based, however bioceramics have also been utilized for this purpose, as well as a variety of materials that have been used as supporting membranes within organ-on-a-chip devices and MPSs.

Hydrogels. Many organ-on-a-chip devices and MPSs incorporate hydrogels as a cell-contacting material.[135] Due to their close resemblance to native ECM, hydrogels can either serve as a 3D matrix for a tissue construct[112] or act as a barrier to mimic tissue interface.[110] Hydrogels also possess additional desirable properties that contribute to their common use in organ-on-a-chip devices, including their optical clarity, which allows for real-time microscopic observation of cell behavior within the gel structures.[136] Most hydrogels are also relatively simple to produce or can be obtained commercially at a relatively low cost.[136]

The excellent cell supporting characteristics of hydrogels are highlighted via their use for this purpose in several commercialized organ-on-a-chip platforms, including the glass-based OrganoPlate system[110,111] that was previously discussed. The silicone-PET composite ParVivo chip from Nortis Inc. demonstrates another successful example in commercializing organ-on-a-chip applications in which hydrogels are a critical part of the devices. The chip consists of cell culture chambers traversed by a channel network (one of the many chip configurations is shown in Figure 6a). It is loaded by filling an ECM-based hydrogel, cell-laden or cell-free, in the chamber and allowing it to polymerize around a microfiber. After polymerization, the microfiber is removed to form a luminal channel within the gel structure that is connected to the ports on the chip for perfusion. To date, a number of models have been developed using the ParVivo chips, including liver,[137] kidney,[138] cancer,[139] and vasculature,[140] highlighting its versatility in various tissue architectures. In particular, the formation of a luminal channel makes the ParVivo chip suitable for modeling tissues with vascular or tubular structures. Despite the presence of silicone-based materials as the structural component, direct contact between the cells/media and silicone is reduced to a large extent by the hydrogel situated in between.

There are additional examples of vascularized hydrogel constructs contained within silicone-based outer structural components developed by sacrificial molding. Kolesky et al.[141] used a fugitive ink containing pluronic and thrombin as a sacrificial template to create 3D vascularized tissues that could be actively perfused for over 6 weeks. To translate this sacrificial molding technique into functional organ-on-a-chip

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applications, Lin et al.[127] fabricated a 3D vascularized proximal tubule model composed of adjacent vascular and proximal tubular channels embedded in a highly permeable and engineered ECM made from gelatin and fibrin within an external silicone gasket structure (Figure 6b). The adjacent conduits were created by bioprinting colocalized microchannels with a temperature-sensitive fugitive ink that was encapsulated as a sacrificial template within the engineered ECM and was subsequently removed by reducing the temperature. By lining the conduits with confluent epithelium and endothelium, the model exhibited renal reabsorption via tubular−vascular exchange akin to native tissue.[127] Notably, the microchannels in this model were circular, which has rarely been achieved in conventional PDMS chips. This system had a large degree of structural complexity that resembled that of the native proximal tubule. The biomimetic design of this model contributed to the improvement of the function and maturity of the cells seeded in the microchannels and increased the model's ability to recapitulate renal reabsorption, due to the flexibility of structural design enabled by 3D bioprinting. Nonetheless, the use of this model for drug testing was limited by the presence of silicone-based materials in the system, such as the gasket surrounding the engineered ECM.

Bioceramic-Based Systems. Three-dimensional bioceramic-based microsystems are currently manufactured by additive manufacturing such as lithography-based ceramic manufacturing[143,144] and laser sintering.[145] These fabrication methods accelerate fabrication processes and reduce cost and production time.[146] Because of heat treatment and crystallization, ceramics exhibit a highly porous and brittle structure.[147] The similarity of mineral structures and mechanical properties of ceramics with native extracellular matrix of the bone tissue offers the potential for bone-on-chip microenvironments.[142,148] One example utilized human bone marrow-mimicking hydroxyapatite-coated zirconium oxide-based Sponceram 3D ceramic scaffolds as the cell contacting material to culture hematopoietic stem and progenitor cells (HSPCs) over 4 weeks (Figure 6c).[142] The device was PDMS-based, but this example highlights the potential for further studies incorporating PDMS-alternative materials to study drug toxicities with bone marrow models. Novel hybrid ceramic-polymer mixtures, such as Ormocomp, offer enhanced optical properties and a wider variety of manufacturing methods (e.g., UV lithography and UV embossing).[149] These ceramic-polymer composites have been used in fabrication of scaffolds for epithelial cells,[150] cardiomyocytes,[151] and fibroblasts.[152]

Device Membranes. PDMS is commonly utilized as a cell-contacting membrane within organ-on-a-chip devices and MPSs due to its optical transparency, elasticity, inertness, ability to withstand mechanical forces, and the ease of controlling its porosity via soft lithography.[153] Membranes for such devices must meet specific requirements regarding transparency, elasticity, porosity, cell adhesion, topography, thickness, and integration into the device.[153]

In terms of PDMS-alternative materials, thermoplastic polymers are frequently used instead of PDMS as device membranes to improve cell adhesion (PDMS membranes often need to be coated with proteins for improved cell adhesion and proliferation) and further limit the absorption of small molecules.[153] Thermoplastics possess generally beneficial membrane properties, including their structural rigidity, biocompatibility, transparency, capacity for cell adhesion, and facile integration into devices. The ease of manufacture of thermoplastics via track-etching[153] and CNC micromilling (which is followed by vapor-polishing to reduce surface roughness)[64] allows for the development of membranes with precisely controlled thicknesses and porosities. There are many manufacturers that sell various thermoplastic membranes of a variety of thicknesses and porosities to be incorporated into organ-on-a-chip devices and MPSs that have led to their broad use. As a result, many of the previously discussed thermoplastic devices materials have been also used as microporous cell-supporting membranes within several MPS platforms, with PC[21,62,65,66,119,153] and COCs[66,154−158] being commonly utilized for this purpose. While there are limited examples of organ-on-a-chip devices and MPSs solely made of these thermoplastics, there are examples of PLA,[159] polycaprolactone,[153] and, notably, PET,[26,78−80] being used as porous tissue supporting membranes.

Where PDMS has a distinct advantage over thermoplastics lies in its elasticity that can be used to mimic dynamic environments, such as the lung[9] or heart.[27] New rapid prototyping strategies for the fabrication of more elastic membranes such as polyurethane[160] and heat or UV-curable polymers, including polyurethane acrylate,[161] PEGDA,[161] and potentially the aforementioned UV-curable elastomers PICO and POMaC, can be used to develop elastic membranes with reduced small molecule absorption. Furthermore, cell contacting hydrogels within organ-on-a-chip devices and MPSs are sometimes considered as supporting membranes that can withstand cellular mechanical forces and better mimic the natural cellular microenvironment over PDMS membranes.

■ PERSPECTIVE AND FUTURE NEEDS

Current organ-on-a-chip platforms have demonstrated great capability to quantitatively and systematically perform drug testing and pharmaceutical studies, but are often hindered by high cost, drug absorption, and low-throughput production. Such limitations can be ameliorated through the development of new materials featuring more beneficial properties coupled with advanced manufacturing and micromachining technologies to produce increasingly sophisticated and reliable platforms that effectively mimic the physiological and structural complexity of native tissues or organs. For example, recent advances in biomaterial science have developed new classes of materials such as nonabsorbent elastomers and transparent polyesters, which can be adapted into advanced techniques such as 3D printing to produce biomimetic tissues or organ structures. Additional advancements must be engineered to overcome some of the issues of the alternative device materials to PDMS, from both biomaterials and manufacturing perspectives.

Many elastomers, such as thermoplastic elastomers and polyurethane, can provide elasticity and optical transparency for microfluidic devices for organ-on-a-chip applications. Thermoplastic elastomers such as SEBS have demonstrated their potential in the fabrication of microfluidic devices via techniques such as 3D printing and injection molding in a high-throughput manner. Polyester elastomers such as POMaC also have tunable properties achieved by adjusting the monomer ratio and UV exposure time. While elastomers such as FEPM, PICO, and POMaC can be molded into customized structures, they are also limited by their molding fabrication method. For example, it is difficult to process FEPM due to its high glass transition temperature and poor

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compression set resistance. The SU-8 master molds used in the molding fabrication are also normally fabricated via soft lithography, which is a time-consuming fabrication process and generally requires equipment in a clean room setting. Ultimately, the material requirements of a wide range of organ-on-a-chip engineering applications would greatly benefit from the development of new nonabsorbent elastomers featuring elasticity, optical transparency, and ease of fabrication.

In terms of thermoplastic polymers, the lack of elasticity in these materials means that they often need to be used in conjunction with elastic materials for tubing, pneumatic pumping systems, gaskets between thermoplastic layers, or to generate dynamic environments that promote cell maturation. The disparity between the Young's moduli of thermoplastics and that of the native ECM of the tissues grown within these devices can have negative effects on cell health and development during culture. This is truly a difficult issue to overcome in solely thermoplastics-based devices, meaning that composite devices combining thermoplastic materials with hydrogels or elastomers as the cell-contacting component may be crucial to improved cellular health for a range of tissues. However, such composites could negate the capacity of thermoplastics for rapid prototyping or high-throughput manufacturing. While elastomers themselves can be manufactured in a high-throughput manner via injection molding, stamping, and waterjet cutting, injection molding and stamping require master molds that take time to generate (and thus are not considered rapid prototyping as per the definition described in Table 2), and the ultimate act of combining elastomers and thermoplastic materials slows the manufacturing throughput rate.

The use of fully gravitationally mediated flow and solvent bonding can work around the tubing and flow issues,[59,63] but these issues are difficult to overcome in solely thermoplastic devices. A rather unavoidable hurdle is the current resolution of the CNC micromilling technique that most thermoplastic-based devices utilize, which limits the topologies that can be generated with these materials. The resolution of micromilling (likely combined with vapor polishing)[64] must be enhanced to construct smoother surfaces at the microfluidic scale. Such smooth, high resolution surfaces are required to generate vessel-like flow channels or alternative topologies capable of producing microphysiological environments more akin to native tissues. The continued improvement of technologies including micromilling and 3D printing, which have greatly developed within the past decade, will lead to more advanced, precise MPSs with enhanced functionality. For example, recent advances in 3D printing and direct laser writing techniques afford the printing of complex 3D nanostructures and topologies within MPS microchannels with COC, which has low absorbance and excellent fluid sealing integrity over PDMS.[162]

Glass- and silicon-based organ-on-chip devices are a promising alternative to PDMS-based systems due to their well-established fabrication techniques borrowed from the electronics industry. Though such devices do not absorb small molecules and are biocompatible, they are often mechanically inelastic and expensive or labor-intensive to produce. To make such devices less costly, recent studies have combined glass, silicon, plastic, or adhesive materials in the same device. That is, the bulk of the device can be made of easy to fabricate tissue culture plastics, resins, or polymeric material, while key components can be made of more expensive glass or silicon. This represents an overall trend in organ-on-chip devices, where multiple materials are combined to address the weaknesses and exploit the strengths of individual materials.[21,60,63,106,108,109,125] The high Young's moduli of glass and silicon and their lack of elasticity often necessitates additional tubing materials for pumping. This limitation has also led to the innovative development of pumpless systems.[28,115] Future work on glass- and silicon-based systems should focus on improving fabrication techniques and combining materials such that devices can be made in a more high-throughput and inexpensive manner.

Hydrogels are widely used in MPS applications due to their desirable properties such as biocompatibility, optical clarity, and low cost.[136] As a material to replace PDMS in the device fabrication, hydrogels offer a major advantage over other, more conventional materials in terms of increasing cell viability and fidelity, due to their physiochemical similarities to *in vivo* ECM. With the development of microfabrication techniques such as stereolithography and sacrificial molding, complex 3D structures can be constructed in hydrogel-based devices,[128,129] which has the potential of overcoming problems associated with the low level of proximity to native tissues of some devices fabricated with other materials. However, compared to materials that can be mass produced, the cost and complexity of fabricating hydrogel-based devices in a high-throughput manner may not place them at an advantageous position in terms of translation. It is also more challenging to perform high-throughput analysis with hydrogel-based devices, which can limit their use in applications such as drug screening. Nonetheless, the high-fidelity tissues resulting from the *in vivo*-like properties of hydrogels themselves and the biomimetic structures on hydrogel-based devices still make hydrogels a promising replacement of PDMS in device fabrication.

More often, hydrogels play another role in organ-on-a-chip devices: facilitating tissue fabrication as a cell-contacting material. They serve this purpose in versatile applications and devices. The most straightforward application is to utilize hydrogels as an ECM by encapsulating cells in them during the seeding processes. Another application is to employ hydrogels as a tissue interface and use them to form a functional barrier by seeding relevant cells on each side.[134] If hydrogels are incorporated within composite devices, the lack of mechanical strength in hydrogels can be compensated for by the other materials. In case the materials that provide mechanical support have shortcomings such as absorbing hydrophobic molecules, hydrogels can, at a minimum, reduce the contact between cells and these materials. For these reasons, hydrogels are likely to serve as a significant cell-contacting or cell-encapsulating material within composite devices.

Overall, there are plenty of other obstacles to be overcome and questions that must be answered as this relatively new field of organ-on-a-chip devices and MPSs continues to grow, including enhancing the similarity of engineered tissues to their *in vivo* counterparts, the development of a methodology to compare differing MPS strategies, and the reduction of plastic waste.

While promising strides have been made using organ-on-a-chip devices and MPSs to recapitulate native tissues, most of these engineered tissues contain a fraction of the various cell types that would be present *in vivo* and have limited control over the spacing of these cell relative to one another. The capacity to achieve this would lead to healthier, more mature

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tissues with intercellular communication more akin to that of the native tissue (which would particularly benefit from the use of nonabsorbent materials discussed herein). While advancements in material design have afforded the development of complex MPSs, this spatial control of a variety of cell types has proven difficult to achieve. A potential solution is through the continued development of automated 3D printing techniques. Increasingly intricate scaffolds are being developed with improved resolution using multinozzle systems that can controllably print cell-laden voxels from a range of material types.[163−165] Park et al.[163] recently 3D printed an airway-on-a-chip with two cell-laden hydrogels, PDMS, and polycaprolactone using four different nozzles. The further development of such techniques to include increasing numbers of materials and cell types in combination with improved resolution and spatial control could significantly enhance the degree to which the engineered tissues of MPSs can recapitulate *in vivo* tissues.

The complexity of attempting to recapitulate multifaceted tissues with engineered systems inherently leads to substantial variability in the assessment of the degree to which such organ-on-a-chip devices and MPSs mimic *in vivo* systems, particularly when various studies utilize devices composed of differing materials. A systematic means of validation within the research community must be established to make any discernible comparisons between MPS strategies.

Another important question is how to incorporate the ability to recycle and reuse materials to decrease the generation of plastic waste. Toward that goal, generating devices that can decompose on demand using renewable materials will be an exciting, albeit ambitious goal. The further development of materials with tunable biodegradability could be utilized for this purpose and could also have a valuable functional role in devices that can be modified by the cells over time. Biomedical and pharmaceutical laboratories are major users of plastics products and generate a significant amount of plastics waste. Many research organizations have programs for recycling of spent tissue culture plastics. We argue here that as organ-on-a-chip devices become a mainstream choice for biological and drug discovery experiments, the amount of organ-on-a-chip waste will significantly increase. Therefore, it is prudent to develop a design strategy that will consider device recycling and reuse as well as sustainable sourcing of materials for device fabrication early on, while the field is still in the niche stage.

CONCLUSIONS

The benefits of PDMS from the perspective of material properties and ease of use in prototyping are currently difficult to replicate with a single material. It is likely that combinations of the PDMS-alternative materials that are reviewed here, which take synergistic advantage of multiples of these material's advantageous properties, will need to be utilized to eliminate the drug absorption bottleneck associated with the PDMS use while also enabling a higher throughput production. The emerging advances in fabrication methods will lead to organ-on-a-chip systems and MPSs with greatly improved capabilities for use in personalized medicine, recapitulating cellular responses to drugs, *in vitro* ADME modeling, and drug discovery. These devices will likely eventually replace conventional *in vitro* and animal models, but this will take time. In the meantime, gradual advances in organ-on-a-chip and MPS technologies will lead to systems that will be able to actualize these larger goals, and the gradual trend toward the use of alternative materials to PDMS for device fabrication is a step in the right direction.

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Notes

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LIST OF ABBREVIATIONS

ADME, adsorption, distribution, metabolism, elimination; API, active pharmaceutical ingredient; BSA, bovine serum albumin; COC, cyclic olefin copolymers; COP, cyclic olefin homopolymers; CNC, computer numerical control; ECM, extracellular matrix; FEPM, tetrafluoroethylene-propylene; HEK, human embryonic kidney; hiPSC, human induced pluripotent stem cell; HPC, hepatic progenitor cell; HSPC, haematopoietic stem and progenitor cell; HuMiX, human-microbial crosstalk;

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hUVEC, human umbilical vein endothelial cell; iPSC, induced pluripotent stem cell; LLG, *Lactobacillus rhamnosus* GG (LGG); μCCA, micro cell culture analogue; MPS, microphysiological system; PC, polycarbonate; PDMS, polydimethylsiloxane; PEGDA, poly(ethylene glycol) diacrylate; PET, polyethylene terephthalate; PICO, poly(itaconate-*co*-citrate-*co*-octanediol); PK/PD, pharmacokinetic/pharmacodynamic; PLA, poly(lactic acid); PMMA, poly(methyl methacrylate); POMaC, poly(octamethylene maleate (anhydride) citrate); PS, polystyrene; SEBS, styrene-ethylene-butylene-styrene; T_g, glass transition temperature; TIL, tumor-infiltrating lymphocyte; T_m, melting temperature

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