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Categorising hybrid material microfluidic devices

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Microfluidic devices are useful tools for a wide range of biomedical, industrial, and environmental applications. Hybrid microfluidic devices utilising more than two materials are increasingly being used for their capacity to produce unique structures and perform novel functions. However, an analysis of publications across the field shows that whilst hybrid microfluidic devices have been reported, there remains no system of classifying hybrid devices which could help future researchers in optimising material selection. To resolve this issue, we propose a system of classifying hybrid microfluidic devices primarily as containing either hybrid structural, chemical, or electrical components. This is expanded upon and developed into a hierarchy, with combinations of different primary components categorised into secondary or tertiary hybrid device groupings. This classification approach is useful as it describes materials that can be combined to create novel hybrid microfluidic devices.

KEYWORDS

hybrid, microfluidic device, microfluidics, manufactoring, fabrication, materials

Introduction

The term microfluidics describes the manipulation of tiny volumes of fluid within channels at the microscale (Akbari et al., 2023). Prior to the advent of microfluidics as a defined field, micro-sized channels were often contained within components of scientific and engineering instruments mostly unrelated to microfluidic applications (Ren et al., 2013; Convery and Gadegaard, 2019). Currently when compared with early microfluidics, microchannels with various geometries are used for many different applications and have huge potential for use within biomedical science (Ramachandraiah et al., 2017; David et al., 2019; Lu et al., 2019; Pritchard et al., 2019; Guzniczak et al., 2020; Xie et al., 2022), industrial processing (Estrada-Osorio et al., 2024; Jayan et al., 2024; Wang et al., 2024; Yi et al., 2024), environmental research (Hill et al., 2022; AlMashrea et al., 2024; Du and Yang, 2024; Sun et al., 2024) and increasingly reaching into other fields (Apoorva et al., 2024; Lei et al., 2024; Reyes et al., 2024). The manufacturing of these microchannels relies upon the use of appropriate techniques, equipment, and materials to produce microfluidic devices consistently and accurately (Ren et al., 2013; Gale et al., 2018; Scott and Ali, 2021; Akbari et al., 2023). New applications often require new channel geometries and the integration of novel components, and it is therefore not unreasonable to suggest that new manufacturing techniques and materials will be necessary to facilitate new microfluidic applications. Hybrid microfluidic devices, comprised of more than one type of material, can be used to meet these requirements. As part of the evaluation of the current state of microfluidic

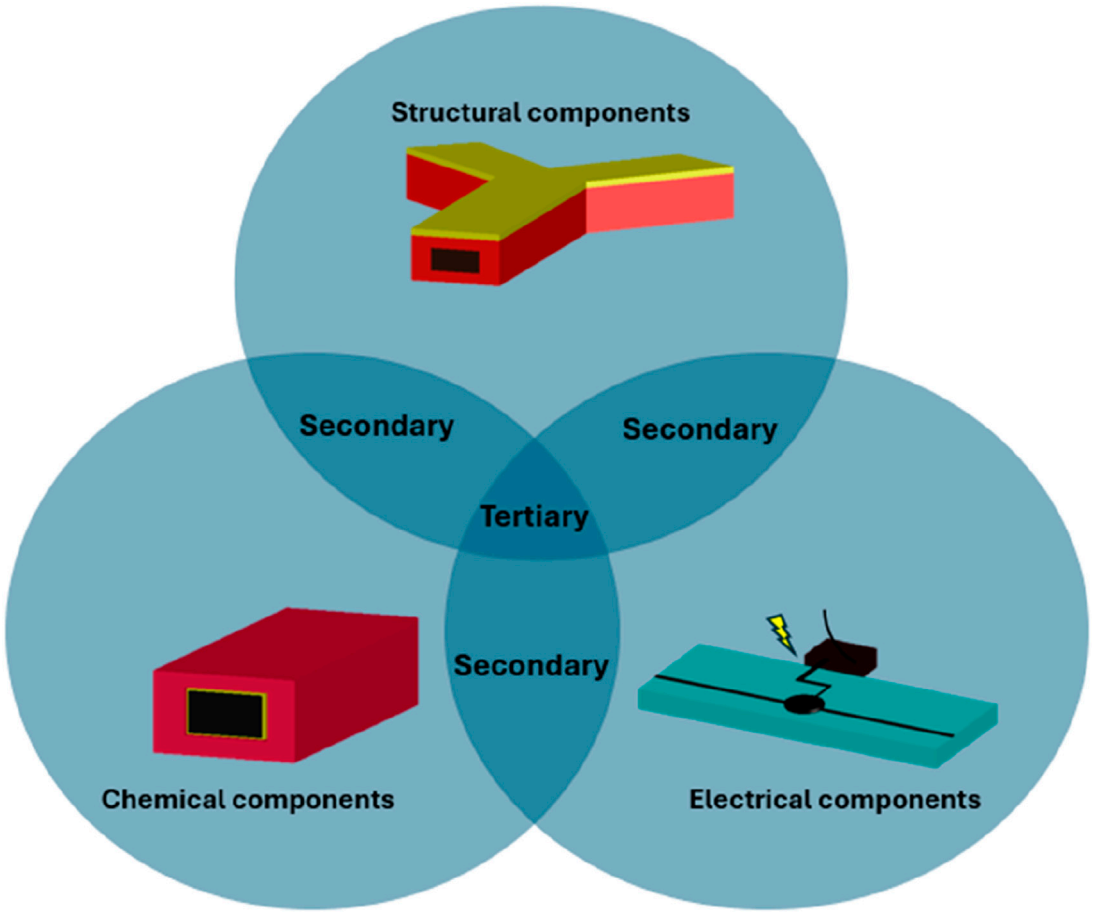

FIGURE 1
Categorisation of hybrid microfluidic devices. The three primary categories of chemical (surface coating in yellow, microchannel in red), structural (materials shown in yellow and red) and electrical (electrodes in black) can be combined to form secondary or tertiary categories of device.

device manufacturing, this mini review focuses on hybrid microfluidic devices that utilise a combination of fabrication techniques and are comprised of at least two materials. Hybrid devices have been reviewed elsewhere but the reviews focus on a summary of the concepts of combining materials (Ren et al., 2013) or require substantial updating in line with current findings (Hou et al., 2017).

Materials and methods

This review expands upon two previous publications (Ren et al., 2013; Hou et al., 2017) that simply described material considerations for use in hybrid microfluidic devices, and for the first time provides a system of categorization of hybrid microfluidic devices. Between February and March 2024, literature searches of PubMed were performed using the following terms: "Hybrid microfluidic device," "PDMS hybrid device," "Composite microfluidic device," "Glass hybrid device," "PMMA hybrid device," and "Polymer hybrid device" with a focus on relevant literature published since 2013.

Although this review aims to provide an update to previous hybrid device reviews, it is not an exhaustive list; examples of devices were chosen to demonstrate both the diversity in material choice and flexibility with which they can be combined for different applications. This was considered of particular importance as it is known that material selection impacts flow, biocompatibility and function of microfluidic devices (Nielsen et al., 2020). A range of papers with different applications were therefore included, and this review will aid researchers in material choice for future microfluidic device designs. The materials related to tubing and fluid connections were considered outside the scope of this review.

Outcomes

Hybrid microfluidic devices have previously been described in a variety of ways and do not have sub-categories to define related device compositions. We propose categorising hybrid microfluidic devices into three primary categories; composites as electrical components; composites as chemical components and composites as structural components.

When considering primary categories, hybrid devices can contain electrical components (comprehensively reviewed in (Tawade and Mastrangeli, 2024)) that are integrated and used

TABLE 1 Categorisation of hybrid microfluidic devices.

Hybrid device sub-category	Material	Composited with	Manufacturing technique(s)	Application(s)	Exemplar reference
Section A: Primary hybrid devices					
Structural	Photosensitive resin	Adhesive tape	DLP-3D printing and stacking	Demonstrating shear stress chip and hydrogel microsphere generation	Qiu et al. (2023)
	PDMS	PMMA and adhesive tape	Photolithography and laser ablation	'Lab-on-a-chip'	Hassanpour-Tamrin et al. (2021)
		Glass	Stereolithography 3D-printing of moulds and casting	Droplet microfluidics, fluid mixing	Vedhanayagam et al. (2023)
			Replica moulding, solvent assisted bonding	Solution exchange and interleukin-2 detection	Pramanik and Suzuki (2019)
		PMMA, adhesive tape and glass	Laser ablation, stacking	Cell encapsulation	Enck et al. (2020)
		PDMS membrane	Soft lithography and chemical etching	Mechanically active organ-on-a-chip	Huh et al. (2010)
		Agarose/agar	Soft lithography and hydrogel injection	Complex gradient of diffusible molecules	Wu et al. (2006)
		Hydrogel, glass, epoxy, and adhesive tape	Photopatterning and stacking	Multifunctional microfluidic systems	Beebe et al. (2000)
		Hydrogel and PMMA	Soft lithography, moulding, laser ablation	3D cell culture	Do et al. (2023)
		Polycarbonate	Soft lithography	Cell culture	Chang et al. (2014)
		Polyvinylchloride	Sol-gel method	'Lab-on-a-chip'	Suzuki et al. (2010)
		Polypropylene			
		PMMA	Soft-lithography, laser ablation and stacking	Production of monodisperse water-in-oil droplets	Nakatani et al. (2020)
		Various thermoplastics	Carbon–nitrogen covalent bonding	Continuous flow polymerase chain reaction	Sivakumar et al. (2020)
		poly (lactic-co-glycolic acid)	Photolithography, moulding	3D cell culture with a blood vessel architecture	Yuan et al. (2012)
		PMMA and cotton	3D printing, soft lithography, thermal bonding	Tumour-on-a-chip	Palacio-Castañeda et al. (2020)
	PMMA	Silicon	Laser ablation	'Lab-on-a-chip'	Capodacqua et al. (2023)
		Silicon	Micromilling, stacking	Microbioreactors	Abaci et al. (2012)
		Polyethylene terephthalate membrane	Micromilling, chemical bonding	Cytotoxicity of drug testing	Nguyen et al. (2019)
		Polybutyl methacrylate	Laser ablation, micromilling, thermal fusion bonding	'Lab-on-a-chip'	Li et al. (2023)
		Thermoplastic elastomers (various)	Laser ablation, thermal diffusion bonding	Organ-on-a-chip/real-time live-cell analysis	Busek et al. (2021)
		Polycarbonate, polytetrafluoroethylene and aluminium	Stacking	Enrichment of exosomes	Hua et al. (2023)
		Acrylate-based resin and adhesive tape	3D-printing, stacking	'Lab-on-a-chip'	Razavi Bazaz et al. (2020)
		Polyimide film	Laser ablation, stacking	'Lab-on-a-chip'	Thaweeskulchai and Schulte (2023)
		Glass, photoresist	Dry film photoresist	'Lab-on-a-chip'	Fan et al. (2018)
		Adhesive tape	Laser ablation, micromilling	'Lab-on-a-chip'	Ku et al. (2018)

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TABLE 1 (*Continued*) Categorisation of hybrid microfluidic devices.

Hybrid device sub-category	Material	Composited with	Manufacturing technique(s)	Application(s)	Exemplar reference
		SU-8	Photolithographic techniques, laser ablation	Cell separation, medium exchange	Carvell et al. (2024)
	Fluoroethylene propylene	Polyimide	Laser ablation, thermal bonding	Fluid mixing	Kim et al. (2016)
	Wax and polyolefins-based films	PMMA or PVC or glass	Laser ablation, thermal bonding	Various biochemical applications, demonstration of bacterial cultivation	Wei et al. (2023)
	Glass	Adhesive tape	Laser ablation, micromilling	'Lab-on-a-chip'	Ku et al. (2018)
		Silicon, aluminium oxide	Anodization of aluminium, deep reactive-ion etching, wet etching, clamping	Gas-permeable cultivation of HACaT-cells	Bunge et al. (2018)
	Polyurethane-methacrylate	Polyurethane-methacrylate coated glass	Casting, conformal coating, UV curation	'Lab-on-a-chip'	Kuo et al. (2009)
	Polyvinyl chloride	Silicon	Laser ablation, jigsaw assembly	Separation of cells	Zhu et al. (2021)
Chemical	PDMS	Hydrogel	Soft lithography	Cardiomyocyte culture	Annabi et al. (2013)
		Zinc oxide quantum dots	Soft lithography	Temperature-sensitive microfluidic device	Zhou et al. (2009)
		Polycaprolactone-collagen membrane and cyclic olefin copolymer	Micromilling, moulding, electrospinning	Lung-on-a-chip	Kanabekova et al. (2024)
	Glass	Acrylate-based photo-co-polymers	Stereolithographic '3P-printing' using a 'Print-Pause-Print protocol'	Not author defined	Ahmadianyazdi et al. (2023)
Electrical	PMMA	Platinum electrodes	Micromilling, hot-embossing, wire embedding	Cell viability analysis	Eades et al. (2023)
	Silicon	Gold nanoparticles	Combining extrusion printing and aerosol jet printing	Amperometric sensing of lactate in sweat	Du et al. (2024)
Section B: Secondary hybrid devices					
Structural, electrical	PDMS	Glass, electrical components	Soft lithography and sputtering	Analyte separation or serotonin detection	Moraes et al. (2012), Shameli et al. (2012)
			Etching, sputtering, soft lithography	Polymerase chain reaction	Kaigala et al. (2008)
			Anisotropic etching of an amorphous bulk material	Various	Mu et al. (2009)
			Various, but mostly the incorporation of electrodes in chip	'Lab-on-a-chip'	Qiu et al. (2003), Li et al. (2008), Zhou et al. (2010)
			Casting	Concentration of analyte	Matsui et al. (2007)
			Photolithography, etching, stacking	DNA sequencing	Blazej et al. (2006)
			Soft lithography, spin coating, aerosol printing of nanoparticles inside microfluidic structures	Authors demonstrated bipolar electrode experiments; other applications possible	Broccoli et al. (2023)
			Photolithography, sputtering, reactive ion etching, printed circuit board	Cell-scale precise temperature control	Lei et al. (2019)
		Glass, polyimide, electrical components	Photolithography, spin coating, electrode patterning	Droplet digital nucleic acid amplification	Coelho et al. (2023)
		PMMA, glass, electrical components	Photolithography, hole punch, mechanical pressure assembly	'Lab-on-a-chip'	Pérez-Sosa et al. (2022)
		SU-8, electrical components	Photolithography	Microparticle manipulation	Guo et al. (2010)
				Lactate monitoring	Wu et al. (2005)

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TABLE 1 (*Continued*) Categorisation of hybrid microfluidic devices.

Hybrid device sub-category	Material	Composited with	Manufacturing technique(s)	Application(s)	Exemplar reference
		Polycarbonate, electrical components	Soft lithography	'Lab-on-a-chip'	Kuo et al. (2003)
		SU-8 and polycarbonate	Soft lithography, moulding and hot embossing	Single cell and manipulation	Chartier et al. (2003)
		SU-8 and quartz	Spin-coating and soft-lithography	Isolectric focusing of proteins	Ou et al. (2009)
		Polyimide, graphene electrodes	Laser ablation, stacking	Wearable devices, point-of-care diagnostics	Thaweeskulchai and Schulte (2022)
		Glass, silicon, polyimide	Stacking, printed circuit board technology	Detection of magnetically labelled protein	Wu et al. (2010)
	Glass	Silicon	Photolithography and wet chemical etching	Polymerase chain reaction	Wang and Burns (2009)
	Polycarbonate film	Glass fibres, Mediprene OF 400M, electrical components	Photolithography, micromachining, or injection moulding	Extraction of nucleic acids from blood	Brassard et al. (2019)
Structural, chemical	PDMS	Agar	Casting and layering	Investigating the oviposition behaviour of *Drosophila*	Leung et al. (2015)
			Soft lithography	Investigating associative learning behaviour of *C. elegans*	Zhu et al. (2023)
		Agar and glass	Replica moulding and stacking	Single cell dynamic studies	Wong et al. (2010)
		Poly (lactic-co-glycolic) acid coated glass	Soft lithography, electrospinning	*In situ* monitoring of stem cells	Hesari et al. (2016)
		Poly-2-hydroxy ethyl methacrylate	Micromoulding, casting	Used to replicate a perfusion microfluidic-based cell culture device	Santaniello et al. (2015)
		Glass and hydrogel	Photolithography, gel casting	Hydrogel matrix degradability-dependent 3D cell invasion models	Trappmann et al. (2017)
		Device 1: Polycarbonate track-etched membrane	Soft lithography, plasma treatment, electroplating, engraving, stacking	*In vivo* detection of small extracellular vesicles	Cong et al. (2024)
		Device 2: indium-oxide coated glass, nickel materials			
		Chromatography paper	Wax printing, PDMS casting	Detection of *Campylobacter* jejuni	Chen et al. (2023)
	PMMA	Poly-2-hydroxy ethyl methacrylate	Micromoulding, casting	Used to replicate a perfusion microfluidic-based cell culture device	Santaniello et al. (2015)
		Paper	Laser ablation and clamping	Detection of IgG	Sanjay et al. (2020)
		Polyethylene terephthalate and paper	Laser ablation and stacking	Detection of cyclamate	Liu et al. (2023)
				Detection of potassium from whole blood	Tseng et al. (2022)
		Paper and glass	Laser ablation, thermal bonding	Enzyme-linked immunosorbent assay	Abate et al. (2020)
		Adhesive tape and polyethersulfone membrane	Laser ablation, stacking	Cleaning of urea/'Lab-on-a-chip'	Gupta et al. (2023)
	Polymer supports	Cell-containing bioinks or hydrogels	3D-printing	3D cell culture models	Richard et al. (2020)
				Cell culture	Krakos et al. (2023)

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TABLE 1 (*Continued*) Categorisation of hybrid microfluidic devices.

Hybrid device sub-category	Material	Composited with	Manufacturing technique(s)	Application(s)	Exemplar reference
	Silicon	Perfouoro copolymer and biomolecules	Photolithography, reactive ion etching, biomolecule conjugation	Detection of carcinoembryonic antigen	Washburn et al. (2009)
	Glass	Polycaprolactone	Oxygen radical exposure of masks composited with glass microfibres	'Lab-on-a-chip', demonstrated colorimetric assay for protein quantification	Bandara et al. (2018)
		PDMS and enzyme-contained hydrogel	Hard and soft lithography, surface activation of glass, enzyme immobolisation	Multi-enzymatic reactions	Simon et al. (2019)
		PDMS and poloxamer	Photolithography, channel coating	Deterministic lateral displacement-dependent cell isolation from breastmilk	Hawkins et al. (2024)
	Photocurable resin	Hydrogel, polystyrene, well plates	Micromilling, 3D printing	Segregated coculture of cells	Berry et al. (2017)
	Cloth	Paper, metal-organic frameworks composited with molecularly imprinted polymers	Printing, 'origami-folding process', clamping	Colorimetric detection of gonyautoxin	Xiang et al. (2024)
Section C: Tertiary hybrid devices					
Structural, chemical and electrical components	PDMS	Paper, glass, electrical components	Soft lithography, laser ablation, stacking	Detection of *N. meningitidis*	Dou et al. (2014)
			Hole-punching, soft-lithography, laser ablation	Detection of *S. aureus* and *S. enterica*	Zuo et al. (2013)
	PMMA	Polymethacrylic acid (as a copolymer), glass, paper and electrode components	Free radical polymerisation and casting of copolymer and dry casting on glass. Biosensor integration into the device	Detection of creatine	Tzianni et al. (2022)
		Polyethylene terephthalate and paper	Laser ablation and stacking	Urine and blood analysis	Laurenciano et al. (2021)
		Microelectrode, carbon nanofibers-decorated gold nanoporous structures	Laser ablation, micromilling, electrode modification	Detection of prostate-specific antigen	Felici et al. (2023)
		Electrical components, aluminium, rubber	Electrode functionalisation, laser ablation, stacking	Detection of miR-122 and potential for diagnosis of drug-induced liver injury	Roychoudhury et al. (2023)
		Electrical components, silicon, glass	Laser ablation, stacking, solvent-assisted bonding	Blood lysate preparation	Haque et al. (2023)
	Glass	Shape memory copolyacrylate, electrical components	Micromoulding, photolithography, casting	Particle separation	Yang et al. (2018)

Note: 'Lab-on-a-chip' refers to a generic application and is included where the author has not stated a particular application. Abbreviations: digital light processing (DLP), polymethyl methacrylate (PMMA), polydimethylsiloxane (PDMS), polyvinylchloride (PVC), ultraviolet (UV).

as sensors or for performing functions such as organ-on-chip monitoring, or cell-matrix interactions within the microfluidic channel. Second, chemical components are integrated into hybrid devices in the form of surface coating materials (reviewed in (Tu et al., 2012)), or as catalysts (reviewed in (Solsona et al., 2019)) for chemical reactions and others. The third category is hybrid devices using composite materials as structural components. Here, two different materials are bonded together to form the walls of the microchannel or as one material acting as a filter within the microchannel, as well as for less functional reasons, such as one material simply acting as a support substrate. When the microfluidic device has a single function, they can be referred to as a primary hybrid device, but different combinations are possible and secondary (containing two types of hybrid components), and tertiary (containing all three types of hybrid components) are also possible to fabricate. This is presented schematically in Figure 1 where examples of microfluidic structures are depicted for each category. In the structural component bubble, an inertial focusing channel is shown and has been fabricated with two materials shown in

yellow and red. The chemical components bubble shows a microchannel structure (red) with a functional coating (yellow) whereas the electrical component bubble depicts a microfluidic device with an integrated component (black circuit).

At least two different materials need to be incorporated for a device to be categorised as a primary hybrid microfluidic device and must form the microchannel walls to be considered a primary structural device. Hybrid devices can be considered primary electrical component devices where an electrical component is integrated but the channel is comprised of only one material. A primary chemical component can be considered a hybrid device where the microchannel is coated with a chemical reagent or the device itself is comprised of a functionalised material to perform the intended application. For the purposes of this review, devices containing reservoirs or those that require the introduction of reagents to the fluidic system are not classified as part of the chemical component category. All other hybrid devices can be considered as devices characterised as having combinations of these primary components and are therefore defined as secondary or tertiary hybrid devices. An extensive, but not exhaustive, list of example hybrid devices across the hierarchy is presented in sections A, B and C of Table 1 with discussions of specific devices of interest.

Section A of Table 1 lists microfluidic devices that can be categorised as a primary hybrid device and can be further divided into devices containing structural, chemical, or electrical hybrid components. Polydimethylsiloxane (PDMS) and polymethyl methacrylate (PMMA) are two of the most commonly used substrates in hybrid microfluidic device manufacture owing to their biocompatibility, flexibility in application, capacity to bond to a wide range of materials and cost-effectiveness (Nielsen et al., 2020). PDMS substrates can be easily modified to generate relatively complex 3D structures employing the widely used technique of soft lithography. However, although PDMS has proven a useful material for many applications, microchannels constructed of PDMS have been shown to absorb small molecules and deform under fluid pressure (Raj M and Chakraborty, 2020). These two issues can impact device functionality where the correct microchannel architecture or the quantification of biomolecules are critical for the application (Hou et al., 2017; Nielsen et al., 2020; Raj M and Chakraborty, 2020). PMMA, on the other hand, does not deform under fluid pressure, can be fully optically transparent, and has higher chemical inertness and greater biocompatibility than PDMS (Gencturk et al., 2017). Despite being one of the most widely used materials in microfluidic devices for cell biology applications, PMMA is not as versatile as PDMS when it comes to generating complex microchannel architectures (Gencturk et al., 2017). Other substrate materials have been used for structural hybrid devices, but their use may be limited by cost, complexity of fabrication technique or issues relating to chemical or biological compatibility. Glass generally has higher costs than thermoplastics but retains excellent biocompatibility, optical transparency and robustness (Hou et al., 2017). Likewise, despite some advantages, silicon lacks optical transparency and photosensitive resins often have poor biocompatibility (Ren et al., 2013; Hou et al., 2017).

As listed in Table 1, hybrid devices utilising PDMS often use soft-lithography and hybrid devices utilising PMMA often use laser ablation for manufacture. Laser ablation is a low-cost, highly replicable fabrication technique and can be used to cut or, etch PMMA at a much higher throughput rate than the use of soft lithography with PDMS (Gencturk et al., 2017; Hou et al., 2017). Generally, where hybrid devices in section A of Table 1 are categorized as having primary electrical or chemical components, a chemically or biologically inert material was used for the microchannel structure to act as a scaffold material for the chemical or electrically compatible material in order to perform their function.

Section B of Table 1 lists secondary hybrid microfluidic devices where materials have been combined to produce a structural channel whilst also simultaneously providing an electrical or chemical functionality. Similarly to primary component hybrid devices, the majority of listed devices are comprised of polymer materials as a base substrate and are often combined with glass, but more recently a range of other materials such as paper, hydrogels and other inorganic materials have also been used. Hydrogels have been used as bioscaffolds (Trappmann et al., 2017) for cell attachment whereas paper has been used as a fluid carrier (Chen et al., 2023). The photoresist SU-8 has extremely high biocompatibility and has historically been utilised as a critical material in microelectronics (Nemani et al., 2013). In some secondary hybrid devices, the coating of microchannels is used to convey a chemical functionality to an otherwise relatively chemical inert microchannel (Hesari et al., 2016) or may contain bioink materials for cell culture (Richard et al., 2020).

The third category, tertiary hybrid microfluidic devices, contain all three of the components discussed previously and a range of examples are listed in section C of Table 1. As before, polymers and glass are the primary substrate materials used in fabrication. Many of these devices utilise the electronic components purely as biosensors although some are used to generate electrical fields to enable a specific function in the device. It is of note that tertiary hybrid devices often have greater complexity and by definition are comprised of more materials than those classified as primary or secondary hybrid devices.

Conclusion

Many microfluidic devices are comprised of at least two materials, but modern multifunctional devices often use more. This review provides an important, but not exhaustive, review of current hybrid material microfluidic devices and proposes a new categorisation system for devices made of multiple materials. Whilst hybrid devices have not previously been systemically categorised, this review aims to provide a new approach to describe intra- and intergroup commonalities, and an insight into why different materials were selected for combination. The development of devices using multiple, diverse materials to achieve complex functionality requires the use of a range of manufacturing techniques, and this review further aims to aid researchers in their selection of materials for future hybrid device fabrication. We acknowledge that as microfluidic device functions increase in complexity with the integration of more materials this review may require updating in the future.

Author contributions

TC: Conceptualization, Data curation, Methodology, Writing–original draft. PB: Supervision, Writing–review and editing. AF: Supervision, Writing–review and editing. HB: Conceptualization, Supervision, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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