

## Review of Commercially Available Microfluidic Materials and Fabricating Techniques for Point of Care Testing

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**Abstract:** During the last two decades silicon and MEMs technology had been the mainstay of early microfluidic devices. However, recent times have brought into focus the need for low cost and readily available materials capable of achieving the expected microfluidics physical and chemical requirements. Also what mentioning is the rapid improvement in microfabrication technology over the years, which has significantly aided new and cheaper ways to produce microfluidic Point-Of-Care-Testing devices commercially or for research purposes. This review article discusses the usefulness of a wide range of available materials and their unique properties suitability in microfluidic applications. Likewise, advantages and drawbacks of manufacturing procedures and outputs of different fabrication methods are also brought into focus. *Copyright © 2016 IFSA Publishing, S. L.*

**Keywords:** Fabrication Techniques, Material Selection, Microfluidics, Point of Care Testing, Lab-on-a-Chip.

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### 1. Introduction

In microfluidics, the properties of Material are very crucial because it affects both functionality and manufacturability. Consequently, the selection process is the foremost consideration for any successful design and fabrication methods of POCT devices. For instance, device performance is critically tied to balancing functional requirements that are related to the physical and chemical properties of the intended material.

#### 1.1. Microfluidic Required Properties

The anticipated physical properties required mostly revolves around mechanical resilience

(modulus of elasticity), visual characteristics (optical) and high-temperature tolerance. Mechanical properties describe the rigidity (hardness) or elastic nature of the device. Hardness features are mostly utilized for the framework where rugged handling is required. Furthermore, since most POCT chips are subjected to relatively high pressures flow when external pumps are utilized. Thus, the designated material are expected to resist rupture. As for the utility of elastic materials, their characteristics are mostly employed in the internal membranes of micropumps and microvalves. The temperature, on the other hand, is needed for chemical reaction or processing done on the chip. For instance, polymerase chain reaction (PCR) relies on repetitive heating and cooling cycles for rapid DNA melting and enzymatic replication, during which the

temperature fluctuates between 52 °C and 96 °C [1, 2]. Thus, a material of considerable temperature resistance is a requirement. Another important feature is the surface properties which dictates the solid-fluid interface relationship. A good example is the surface interaction between microchannel surfaces and active fluids (reagent). These interactions can be described physically as surface hardness and roughness which are the main factors that determine hydrophobic or hydrophilic characteristics. When the surface is hydrophilic capillary flow is enhanced, while the opposite applies to hydrophobic surfaces. Although, in recent times innovative methods such as surface modification techniques are being employed to treat specific surface to adhere specific surface requirements. Regarding requirements, hydrophilic patches are required to accelerate flow, while hydrophobic patches for stopping fluid flow [3]. A common surface modification technique is plasma treatment [4]. Applications involving optical properties is usually associated with fluorescence which is the emission of electromagnetic radiate

In in this case Ultra Violet (UV) light to aid chemical reaction or DNA detection. This real-time fluorescence detection system [5-7] are usually employed lab-on-a-chip applications. Thus, the degree of material transparency becomes highly significant. Chemical resistance (inertness),

antifouling and disposability are also vital requirements in material selection. Chemical resistance involves a material surface reaction to chemicals (organic solvent, water, etc.) as shown in Table 1. The main interest in this reaction is the whether the contact surface and overall nature of the material is altered or not. This alteration relates to absorption and adsorption of the small molecules of solvents in contact with the material surface. Whereas, when the concerned chemicals or reaction are of biological connotations the term biocompatibility is used in reference to the material. For instance, absorption of organic solvents in PDMS fabricated chip causes swelling of the chip, which results in distortion of the microchannels [8-9]. Therefore, the fluid flow within the channels are impaired and might lead to building up of excessive back pressure in the pumping mechanism. Similarly, antifouling otherwise known as Protein fouling is the accumulation of proteins on a surface, especially in microchannels. Fouling of surfaces in microfluidics devices, predominantly, when the protein or enzymatic solutions are often used creates both restrictions of flow channels of very small dimensions and also alter the surface chemistry of the channels [10-11]. The above-listed surface modification techniques are usually applied to improve microfluidic functionalities.

**Table 1.** Overview of physical properties for common microfluidic polymers and material [107].

Polymer/Material	Acronym	$T_g$ (°C)	$T_m$ (°C)	CTE ( $10^{-6}/^{\circ}\text{C}^{-1}$ )	Tensile Strength (MPa)	Optical Transmissivity		Water Absorption (%)	Acid/Base Resistance	Solvent Resistance
						Visible	UV <sup>a</sup>			
Cyclic olefin (co)polymer	COC/COP	70-155	190-320	60-80	60	Excellent	Excellent	0.01	Good	Excellent
Polymethylmethacrylate	PMMA	100-122	250-260	70-150	70	Excellent	Good	0.3-0.6	Good	Good
Polycarbonate	PC	145-148	260-270	60-70	70	Excellent	Poor	0.12-0.34	Good	Good
Polystyrene	PS	92-100	240-260	10-150	40	Excellent	Poor	0.02-0.15	Good	Poor
Polypropylene	PP	-20	160	18-185	40	Good	Fair	0.10	Good	Good
Polyoxymethylene	POM	60	190-210	11	73	Poor	Poor	0.22	Good	Good
Polyetheretherketone	PEEK	147-158	340-350	47-54	96	Poor	Poor	0.1-0.5	Good	Excellent
Polyethylene terephthalate	PET	69-78	248-260	48-78	55	Good	Good	0.1-0.3	Excellent	Excellent
Polyethylene	PE	-30	120-130	180-230	15	Fair	Fair	0.01	Excellent	Excellent
Polyvinylidene chloride	PVDC	0	76	190	54	Good	Poor	0.1	Good	Good
Polyvinyl chloride	PVC	80	180-210	50	51	Good	Poor	0.04-0.4	Excellent	Good
Poly sulfone	PSU	170-187	180-190	55-60	-	Fair	Poor	0.3-0.4	Good	Fair
Polydimethylsiloxane	PDMS	-125	-40	310	2.24	Excellent	Excellent	0.05	Good	Good
Soda-Lime Glass	Silica	564	1000	9.5	74	Excellent	Excellent	0	Good	Good
Epoxy Resin	SU8	50-200	380	52	34	Excellent	Excellent	0.65	Good	Good

Material Disposability comes in two folds which can be identified as cost and eco-friendliness. Material cost plays a major role in chip prototyping and commercialization because at low-cost microfluidic POCT device prototyping research is made easier while commercialization of new design products is aided by affordability. The factors that determine cost are the material availability and cost of synthesis or production. Inexpensive materials tend to be ubiquitously available in the market while at the same time easy and cheaper to synthesize. Since polymers commonly used in microfluidics

device fabrication are non-biodegradable, recycling becomes the best effort that helps reduce the high rates of plastic pollution. Then again there have been the recent use of biodegradable polymers [12] in microfluidics device in tissue engineering [13-14].

## 1.2. Silicon

Before the rapid growth of interest in polymer materials for MEMS, silicon was the most important material for microelectronics because of its

semiconductor properties. Although brittle when stressed to the point of fracture, silicon is remarkably effective as a mechanical material [15]. The crystalline structure of silicon inhibits gas permeability; which is one of the necessary characteristic vital for cell culturing in microfluidic systems [16]. It also exhibits linearly elastic behaviour below its yield strength with no hysteresis and suffers no plastic deformation or creep except under very extreme temperatures well beyond relevance to microfluidic applications. As a result, their high material stiffness makes it very difficult for the fabrication of mechanically movable microfluidic structures (diaphragms) required for microvalves and pumps; which fair better under soft and flexible materials. Though, silicon is still a utilized material for moulds replication in microfluidics.

Silicon is also prevalent in microfluidics in the form of polysilicon (i.e., polycrystalline silicon) and amorphous silicon. In both cases, the silicon is typically deposited as thin films by vapour deposition, and can be doped for electronic device functionality. Polysilicon is used in many diverse ways for surface micromachined sensors and actuators. For example, in the case of actuation, polysilicon has been used for electrostatic diaphragms [17] and as heating elements for micropumps. Properly doped polysilicon is also effective for sensing elements based on capacitive displacement [18] and piezoresistive strain measurement. Another unique aspect of silicon is that it can be made highly porous with good uniformity by an anodic electrochemical etch process. Porous silicon has an extremely high surface-to-volume ratio, which is particularly advantageous for applications with surface reactions involving catalysis, adsorption and desorption [19].

### **1.3. Glass**

The term glass usually refers to materials that are predominately amorphous silicon dioxide ( $\text{SiO}_2$ ), also known as silica. Varieties of glass are made by including other compounds such as sodium carbonate, calcium oxide, and boron oxide to produce different thermal, mechanical, and optical characteristics. Like silicon, glass is rigid, dimensionally stable (thickness of 30  $\mu\text{m}$  can be handled) and relatively brittle. Many common categories of glass are optically transparent, making glass favourable for applications that require imaging or optical methods of detection for fluids particles. Glass is a very convenient substrate for microfluidic devices because it is readily available and typically cut into rectangular slides or circular wafers. For applications such as capillary electrophoresis, glass microchannel chips are routinely produced as either commercial off-the-shelf products or even semi-custom layouts. Unless specifically engineered for electrical conductivity, conventional glass exhibits sufficient electrical insulation such that it can serve

as a substrate for direct patterning of conductive metal lines and functional electrodes [20-21].

A common way of creating channels in glass substrates is by wet etching, typically with a concentrated hydrofluoric acid. Wet etching of glass occurs isotropically and typically produces rounded profiles with low aspect ratio. Holes and channels in glass substrates can be fabricated by ultrasonic drilling and laser ablation. There are also formulations of photosensitive glass that exhibit spatial etch selectivity when exposed to UV radiation through a mask [22]. Although the majority of glass microfluidic devices use slides or wafers, glass in other forms can also be used to fabricate channel-like structures using spin-on-glass [23] or sputtered films. A good example of a commonly used derivative is borosilicate glass. It has an excellent ability to resist strong acids, saline solutions, strong oxidizing and corrosive chemicals. In the same way, their chemical inertness exceeds that of most metals and other materials because at temperatures above 100°C they still retain their inertness for a long period. Economically, they are easily mass produced and readily available in differs thickness.

### **1.4. Fused Silica Quartz**

Fused silica quartz is dissimilar to quartz which is a crystalline material whereas fused silica quartz is amorphous, just like other glass forms they are that are mostly made up of silica in its non-crystalline form. They can be manufactured using several different processes. Prominent amongst this is a vitreous method (splat-quenching or melt-quenching) used to form the quartz by heating the material to its melting point and rapidly cooling it. While the fused used Silica is formed by fusing high purity silica in a specially designed furnace. The overall procedure is carried out at extremely high temperatures, over 500 °C. The microfluidic device fabrication processes with this material are similar in precision to the ones used in the electronics industry. For instance, the channels for fluid flow are etched into materials by photolithography processes. While in the case of multi-patterned layers can be very accurately aligned and fused together. Recently Engineers at Dolomite can now etch optically smooth features with depths of up to 150 microns which is far deeper than most available solutions in the marketplace which can only offer depths in the area of 20 microns [24].

In comparison to glass, quartz is much harder with great thermal shock resistance. It also has an excellent chemically inertness; fused silica quartz can handle the high concentration of acids except hydrofluoric acid even at low concentrations. They do have superior optical properties (UV transparency) in comparison to glass and can be used for applications such as flow cytometry (cell sorting and cell counting). For example, Institute of Photonic Technology in Germany, in collaboration with the

Department of Internal Medicine have developed a Quartz microfluidic chip that can be used for tumour cell identification using Raman spectroscopy in combination with optical traps [25]. Some other benefits include non-auto-fluorescent and non-porous characteristics making it a preferred material for applications in the POCT.

### **1.5. Metals**

Metals are obviously distinguished by having significantly higher electrical conductivity than other categories of materials used in microfluidics. Accordingly, metals are frequently used for electrical functional components such as electrodes, conducting lines, or signal interface contacts. As conductors of electricity, metals may also be used to modify electromagnetic fields, which may subsequently be used in novel ways for applications such as biological cell manipulation [26]. Another functional merit for metals is high thermal conductivity. For example, a heat spreader based on micro heat pipe design has been constructed from layers of copper and brass for microprocessor cooling [27-28]. The relatively high mechanical strength of metals favours their use for high-pressure applications, compared to polymer materials. Some metal alloys that have favourable magnetic properties have been incorporated into functional components such as nickel-iron rotors for active mixing [29-30]. Magnetic components have also been combined with deformable polymer structures for functionality as micropumps [31] and microvalves. Some microfluidic devices also take advantage of shape memory alloys. Nickel-titanium (NiTi), which changes from its austenite phase to its martensite phase upon cooling and the corresponding shape change, can be used for device actuation.

Gold, nickel, and copper are among the most commonly used metals in microfluidic devices. Gold is often the material of choice for electrical purposes because of superior resistance to corrosion and oxidation, even though other materials such as copper have lower electrical resistivity ( $1.7 \times 10^{-6} \Omega\text{cm}$  for copper versus  $2.2 \times 10^{-6} \Omega\text{cm}$  for gold). Nickel, copper, and alloys based on nickel or copper are favourable for structures made by electroplating and electroforming. Single nickel electroforming step is a good example of commercially viable means of making a metal microfluidic structure such as ink-3Djet print heads [32]. In contrast to gold and copper, the much higher resistivity of platinum ( $10.6 \times 10^{-6} \Omega\text{cm}$ ) makes it favourable for resistive heating. Other metals such as aluminium and tungsten are prevalent in microelectronics but less common in microfluidic devices.

Recent publications have shown that gold, silver and gold-silver alloy nanoparticles [33] now offer an alternate solution to optical detection through resonant light scattering spectroscopy (RLS) [34]. This unconventional route approaches the perspective of gold and silver particles as substitutes for

fluorescent probes in certain microfluidic applications. Still, the possibility of dark field RLS detection [34] and quantitation of metal nanoparticles in POCT devices are opening thought-provoking potentials for the advance development of microfluidic detection systems [35-36].

Another important role of metals in microfluidic device fabrication is tooling. Even if the final device made of a different material, it is sometimes beneficial to have finely patterned tooling to transfer the relevant geometry by hot embossing or other moulding technique. This facilitates more rapid high-volume manufacturing with good repeatability. One approach, for example, is to begin with laser micromachining of patterned tooling in a thin metallic sheet, then to transfer the pattern by hot embossing onto a thermoplastic (PMMA) master, and to complete the process with the casting of PDMS atop the PMMA master [37].

### **1.6. Paper**

Paper-based “microfluidics” or “lab on paper,” provides an innovative system for manipulation and analysis of fluid for a variety of applications. They are typically made up of cellulose or cellulose polymer that possess excellent compatibility trait with several medical diagnostics applications and can be chemically modified to integrate an extensive range of functional groups that can be covalently bound to DNA or proteins [38-39]. Just like most papers they are easy to stack, store, transport, depose (burning) and most especially available in a wide range of thicknesses (0.07-1 mm) [40]. Besides, unlike conventional microfluidics, its preference to fluid flow by capillary driven forces makes it requires little or no ancillary pump which often require external power assistance.

These systems integrate some of the capabilities of conventional microfluidic devices with the simplicity of strip diagnostic tests [41-42] and can be referred to as micro-pads ( $\mu\text{PADs}$ ).  $\mu\text{PADs}$  are very significant in comparison because they provide bio-analyses that are more rapid, less expensive, and more highly multiplexed than contemporary analyses. They require only minute volumes of fluid and very minimal external supporting equipment or power because fluid movement in  $\mu\text{PADs}$  is controlled principally by capillarity and evaporation. Their Features can be identified by a variety of 2D and even 3D microfluidic channels that have been created on paper to confine and manipulate fluid flow within the predesigned pathways on paper [43]. Unlike orthodox microfluidic devices that have their microchannels fabricated by etching or moulding channels into PMMA, glass, PDMS, or other polymers; instead  $\mu\text{PADs}$  make use of patterning sheets of paper into hydrophilic channels constrained by hydro hydrophilic cellulose fibers of paper allowing aqueous fluids to wick along the channels. The flow rate of the wicking is contingent on the

characteristics of the paper, ambient conditions (temperature and relative humidity) and most especially dimensions of the channel. Furthermore, the cellulose matrix can be combined with conducting carbon or metal fibers [44]. This innovative configuration provides electrically conducting or magnetically responsive patterns on the  $\mu$ PADs. The microfluidic paper technology is already used extensively in as a point-of-care device in developing countries where healthcare and disease screening is expensive and not readily available due to low-infrastructure and limited trained medical and health professionals [44-45].

### **1.7. Polymer**

As a result, of the growing demands for cheap and disposable POCT devices during the early 1990s, the selection of suitable materials has gradually shifted from the conventional materials such as silicon and glass towards polymers. This gradual change which was eased through by the advent material technological progress can be considered a major innovation in the field of microfluidics POCT, which is primarily needed in various biomedical and clinical applications.

Compared to other types of materials, polymers represent a wide variety of material characteristics for microfluidic devices [46-47]. They have relatively low mechanical strength, low melting point, and high electrical resistance. The main advantage that polymers offer is that they can be engineered or synthesized to exhibit certain chemical and physical properties required for targeted functionality such as optical transparency, chemical resistance, stiffness, critical surface tension, etc.

### **1.8. Polymer Chemical Classification**

Polymers chemical classification are based on monotonous structural blocks called monomers that are capable of being bonded chemically to other molecules in long chains to form large-sized molecules. These macromolecules or polymers can be used to create diverse material properties from their monomers by polyaddition [48] reaction or polycondensation [49]. The most frequently used monomer chemistries Acrylates and vinyl polymers, Epoxy resins, Thiol-enes, Polyurethanes, Siloxanes.

#### **1.8.1. Epoxy Resins**

Epoxy polymers are typical derivatives of glycidyl or oxirane group and can be created from synthesis of Bisphenol A epoxy resin, Bisphenol F epoxy resin, Bisphenol F Novolac epoxy resin, Aliphatic epoxy resin and Glycidylamine epoxy resin [50]. Further details of the chemistry engineering of epoxy can be found in this textbook [51]. A good example of an epoxy-based polymer is SU8, which is

a commonly used substrate for making a master mould for photolithography technique. The “8” in SU-8 stands for the eight epoxy groups in a bisphenol-A novalac glycidyl ether a single molecular structure. SU8 photolithography produces a Good adhesion and high aspect ratio negative photoresist that allows for the creation of deep channel microfluidic structures and as well as variant depth through multiple UV light exposure [52] (this technique will be discussed in the microfabrication section). In addition, they are also suitable polymers material choice for prototyping techniques such as stereolithography [53-54].

#### **1.8.2. Thiol-enes**

The thiol-ene reaction is acknowledged as a click chemistry reaction given the reactions' maximum yield, fast rate, stereoselectivity and thermodynamic driving force [55]. They are compounds with sulphur hydrogen groups also known as alkene hydrothiolation; which is an organic reaction that forms alkyl sulphide [56]. They are commercially produced from mixing monomers such as trithiol with triene or tetrathiol with triene in varying ratios, which are calculated on the amount of free thiol and allyl (ene) groups in the monomer structure [57]. Subsequently, the mixed ratios can then be cured rapidly under UV light through free-radical polymerization at ambient temperature and pressure [58].

Thiol-ene chemistry are now seen as PDMS substitutes in soft lithography [59-61] for bioanalytical applications because they are not prone to protein fouling [62-63] to swelling upon contact with organic solvents [64], absorption of small hydrophobic molecules [65]. Most importantly high elastic modulus (PDMS is frequently restricted to comparatively low working pressures of about 1 Bar [66]. They are mostly utilized in microfluidics for surface engineering and microchannel patterning [67].

#### **1.8.3. Acrylates and Vinyl Polymers**

Acrylate monomers are typically derivatives of acrylic acid [68] which consist of vinyl hydrogen and the carboxylic acid, while vinyl monomers are consist of vinyl group [69] or ethylene. However, acrylates are industrially easier to synthesize than pure vinyl polymers which are toxic and difficult to handle. An example of a simple acrylic acid synthesise is the methyl methacrylate which has its vinyl hydrogen and carboxylic acid hydrogen substituted by methyl groups to form poly(methyl methacrylate) (PMMA) [70], typically known for their transparency. On the other hand vinyl, chloride can be polymerize [71] with the assistance of a radical a catalyst to form of polyvinyl chloride (PVC) which is widely used material.

#### **1.8.4. Polyurethanes**

Polyurethanes (PU) polymers also known as polycarbonates are created by the reaction of two monomers di-isocyanate and a polyol that contains containing hydroxyl groups in the presence of a catalyst or by ultraviolet light stimulation [72]. There are of high relevance in microfluidic prototyping because of their suitability in the creation of molds [73] and as structures [74] in microfluidic devices. This polymer also serves as another alternate to PDMS because they are not prone to protein fouling especially when biofluids are involved for example blood [75]. Nevertheless, they are relatively expensive and mostly transparent.

Polyurethanes robust reaction mechanism can be tailored to fit two typical forms in microfluidics which include elastomers and surface coatings. Elastomeric polyurethane (PU) which can be derived from bio-source such as castor oil (CO) [74]. This elastomer can be used to produce microvalves elastomer in microvalves that can be integrated with microfluidic devices [76]. Moreover, microchannel formation and sealing (both reversible and nonreversible) is easily attainable in PU components using partial curing [74].

One the other hand the coating specification applies to surface modification for good compatibility with a wide range of solvents and chemical resistance.

#### **1.8.5. Siloxanes**

Siloxane polymers have mostly been used in microfluidics device prototyping for last two decades. They are chemically a class of polymers that exhibit an interchanging silicon–oxygen polymer with each pair of silicon centres separated by one oxygen atom to form backbone chains that are very elastic. Consequently, this renders most siloxanes as elastomeric materials. A principal example is a polydimethylsiloxane (PDMS) that methyl groups as the main polymer backbone. PDMS are of significant importance due to their low critical surface tension, flexibility, chemical resistance and surface hydrophobicity in nature. This defining features of PDMS comprises of the polymer matrix (often aromatic siloxanes) and a curing agent which activates ring opening polymerization or similar crosslinking. This process usually involves the use of moulds or a solid master that gives the expected shape of the PDMS when cured. This process is known as casting [78].

A substitute method of curing similar to thiol-ene involves the use of a catalyst (typically a platinum catalyst) on a mixture of SiH and vinyl terminated polysiloxanes. A detailed analysis of the synthesis and characterization of siloxanes are found in this text [51].

#### **1.9. Polymer Physical Properties**

The physical and mechanical properties of the physical and mechanical properties of polymers can be categorised into three rudimentary temperature dependent parameters in the form of glass transition temperature ( $T_g$ ), heat distortion temperature (HDT) and decomposition temperature (TD).

Glass transition temperature ( $T_g$ ), which is of considerable technological importance has its derivation from the molecular compartment of the polymer material. It's an amorphous change unique to only polymers that involve reversible hardened or softening above or below a threshold temperature. As the polymer absorbs heat, up to a certain temperature the intramolecular friction holding each fragment/monomers in the polymer chain is weakened by the relative motion as a result of absorbed energy. At this point already hard polymers will have larger segments of their polymer chain moving freely, leading to a substantial softening of the material. On the other hand, when already soft polymers cooled below their  $T_g$  they become hard and brittle, like glass. The case of heat distortion temperature (HDT) describes the maximum temperature for which a polymer material susceptible to mechanical failure from stress as it would simply give way beyond this temperature. The last important parameter, decomposition temperature (TD), is the point at which the physical characteristics of the polymer is permanently altered as a result of the total breakdown of the polymer chains. At this point in temperature, the polymer is known to decompose.

##### **1.9.1. Thermosets (Duroplastic Materials)**

These materials often called resins and are usually liquid at room temperature. They typically formed from a corresponding monomer that undergoes a crosslinking by a chemical reaction, photoinitiator or thermo-initiator for polymerization. Initiated chemical reaction is done by mixing the monomer with a curing agent. While crosslinking initiated physically by light (photoinitiator) are typically UV irradiation and curing induced at a temperature typically above 200 °C [79-80] are a good example of thermo-initiator reaction. All these curing (cross-linking) processes involve an irreversible chemical reaction and once taken place the polymer becomes rigid with a significant increase in molecular weight and higher melting point. Furthermore, the crosslinking forms close-fitting and solid three-dimensional network that are usually stable at room temperature. When subjected to unrestrained heating, the cured material results in reaching the decomposition temperature earlier than the melting point which will eventually decompose the polymer. Consequently, a thermoset material cannot be melted and re-modelled after undergoing curing process because their  $T_g$  is typically rather high and close to

the decomposition temperature (TD) so, therefore, they burn instead of melting. As a result thermosets cannot be recycled therefore less eco-friendly. Well on the brighter side they do possess good dimensional stability, thermal stability, chemical resistance and electrical insulation properties, which makes them suitable for fabrication of microfluidics devices.

Archetypal examples of thermoset polymers in microfabrication are the resist materials for microfluidic applications, especially the photoresist (negative & positive) SU-8 (see Photolithography).

### **1.9.2. Elastomers**

Elastomers typically known as silicone rubber are polymers with glass transition temperatures characteristically lower than the normal operating room temperature. When they are cooled to their Glass Temperature, there is less mobility between the polymer chains that eventually results in the material becoming brittle and less elastic. Just as their name (elastomer/rubber) they are known to undergo elastic deformation as a result of very weak inter-molecular forces with generally low Young's modulus and high failure strain rate in comparison with other materials. They also share similar characteristics with thermoset with regards to TD even though thermoplastic elastomer does exist. Engineered thermoplastic elastomers (TPE's), are one of the most multipurpose polymers available [81] because of the combined performance properties of thermoset rubber with the processing ease of today plastics. As a result, there is versatility of design options and better cost-reduction opportunities. The most commonly used elastomer in microfluidics prototyping is PDMS, and recently, fluorinated elastomers (FKM/FFKM) [82-84] have gained significant traction in the community. These materials exhibit number of properties that make them excellent materials for microfluidics that include very low critical surface tensions, high biocompatibility and outstanding chemical resistance. As well most of these fluorinated elastomers have their glass transition temperatures well below room temperature.

Since elastomers are usually soft, flexible and able to deform elastically without extensive pressure they are therefore an ideal material for active microfluidic components such as membrane and mechanical valves needed for microvalves or micropumps. Furthermore, they are also suitable for the creation of deflectable channels in regards to TPE material [81, 85].

### **1.9.3. Thermoplastic Materials**

Thermoplastics Compared to thermosets is made up of linear molecular chains not cross-linked. This polymer chain configuration supports easy movement within the polymer chains bulk as intermolecular

forces weaken rapidly at high temperatures. Most thermoplastics do have high molecular weight and with unrestricted heating at temperatures above their  $T_g$ , they melt into a viscous liquid and then solidifies upon cooling [86], unlike thermosets that decompose. Thermoplastics, therefore, can be moulded or reshaped by heating. There two classes of this polymer. First of all, is the amorphous thermoplastic, which has intermingled molecular chains with no crystalline structure present within the material. This polymer Chain disorder leads to intermolecular twisting and coiling since there is no crystalline structure present. Consequently, this means the materials are susceptible to failure above the glass their transition point due to low Heat distortion temperature, HDT. In additional, there are known for mostly their transparent or translucent, low tendency to creep, good dimensional stability, low tendency to warp, brittleness, low chemical resistance sensitive to stress cracking.

On the other hand, Semi-crystalline is denser than amorphous since the degree of crystallinity is proportional to density measurement [87-88]. This thermoplastics have some macromolecules in the form of crystalline structures dispersed throughout the material. As a result of this crystalline regions, the materials have a tendency to be very hard (resilient intermolecular forces); and capable of withstanding mechanical stress above the glass transition temperature (high Heat distortion temperature). Their material properties are characterized by being translucent or opaque, good fatigue resistance, toughness, and good chemical resistance. Table 2 shows various thermoplastic materials and their corresponding characteristics.

## **2. Material Bonding Properties**

Bonding in microfluidics is a vital process that involves sealing two or more substrate arranged in a specific configuration that forms the internal environment of the Lab-on-a-chip (LOC) devices. This internal environment consists of microfluidic elements such as microchannels, mixer, valves, reaction chambers, fluidic connectors (inlet port and exit port). The Bond strength which is a significant factor in the sealing process can be reversible (relatively weak) but most commonly used applications are irreversible (permanent). Similarly, the bond interface is also another significant factor for consideration because it must provide appropriate chemical or solvent compatibility to avert degradation during usage, without compromising the dimensional integrity of the microchannels as a result of deformation during the bonding process.

The main concerns for the bond interface include surface chemistry, optical properties, material compatibility and uniformity of the channel sidewalls. Likewise, the already bonded substrates required to constraining the reagents, solvents and bio-samples in specific volumes while also

preventing unrestrained dispersion of liquids along wettable areas. Furthermore, External contaminants (dust, etc.) are prevented from coming into the chip. Likewise the anticipated fluid waste are restricted from going to outside world (biohazard). Finally, evaporation which is the main antagonist of fluid sample and reagents in the chip are brought to a

minimal level especially during thermochemical reactions. The Selection of bonding techniques depend mostly on the materials characteristics and type of constraints imposed by the application. Several bonding techniques are available, both past and recent are covered in this review journals [122-124].

**Table 2.** Polymers and other microfluidic materials with their relative commercial viability and general microfluidic use [115].

Polymer/Material	Price	Commonly Used Microfluidic Applications
Cyclic olefin (co)polymer	Low	Has been utilized, amongst others, as material for microfluidic devices in liquid chromatography [72] and blood typing [73].
Polymethylmethacrylate	Low	Has been used for the Fabrication of devices for on-chip electrophoresis [74] and for the separation of DNA [75]. PMMA exhibits very low auto fluorescence, making it an excellent material especially suitable for optical applications.[76].
Polycarbonate	Low	Has been used, among others, for the creation of microfluidic mixers [77] and devices for DNA amplification [78].
Polystyrene	Low	Has been used, among others, as substrate material for cell culture devices [79] and cell growth studies [80].
Polypropylene	Low	Has been used expansively as substrate material for optical biosensors in CD format [81] and is generally used as a material for membranes on chip [82].
Polyoxymethylene	Low	Mostly used as material for microfluidic moulds [83-84] and particle separation [85].
Polyetheretherketone	High	Has been used for the creation of microfluidic networks for capillary electrophoresis [86] and fluidic pre-concentration of analytes for mass spectroscopy [87].
Polyethylene terephthalate	Low	Has been used, amongst others, for the Fabrication of devices for capillary zone electrophoresis [88-89].
Polyethylene		
Polyvinylidene chloride	Low	Has been used, among others, for the creation of microfluidic pumps [90] and for capillary electrophoresis devices [91].
Polyvinyl chloride		
Polysulfone	High	Has been used for the encapsulation of droplets in microfluidic devices [92] and as material for filtration [93].
Polydimethylsiloxane	Medium	Mostly used in Microfluidics chip prototyping due to its affordable processing with fast turnaround times and also suitable for the creation of deflectable channels, membranes and mechanical valves [94-97].
Soda-Lime Glass (Slides)	Low	Mostly Used in Microfluidics prototyping with PDMS (good bonding substrate), creation of electroosmotic flow chips [98-100].
Epoxy Resin (SU8)	High	Used in electroplating moulds, sensors creation, actuators, and most especially, SU-8 can be used to create structures (microchannels) with dimensions ranging from millimeters to hundreds of nanometers [101-103].

However, this thesis discusses the commonly used techniques in microfluidics substrate bonding which include adhesive bonding, thermal fusion bonding, solvent-based bonding, localized welding and Surface treatment and modification.

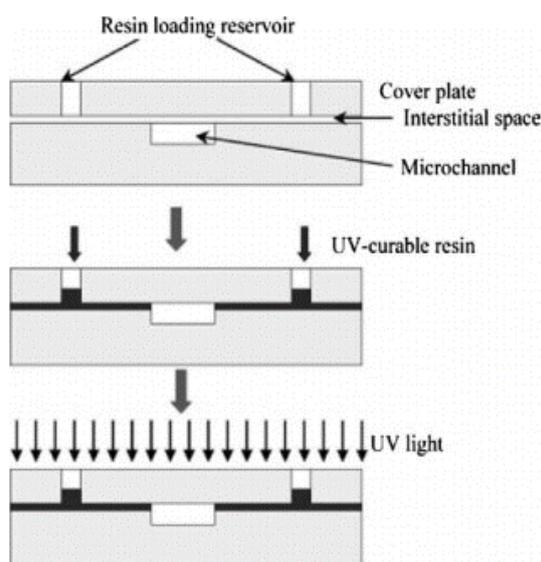
In general microfluidic bonding techniques can be characterised as either indirect or direct. Indirect bonding involves the use of an extra layer apart from the substrates in concerned. This layer is an adhesive that seals the two substrates and their encapsulated internal microfluidic elements together by charge interactions [125-126]. The charge interactions can be a result of chemical (covalent) bonding or van der Waals forces [126-127]. In contrast, direct bonding methods mate the substrates by molecular

entanglement, which is mechanical interlocking of two surfaces by relative diffusion between them. This process is done without any additional materials added to the interface. It is distinguished by its ability to produce microchannels with homogeneous sidewalls [128].

## 2.1. Adhesive Bonding

[Most commonly used adhesive are UV curable [129], with the bonding process performed by applying a thin layer of a high viscosity liquid adhesive which is then cured by UV light irradiation. This process is illustrated in Fig. 1 which shows

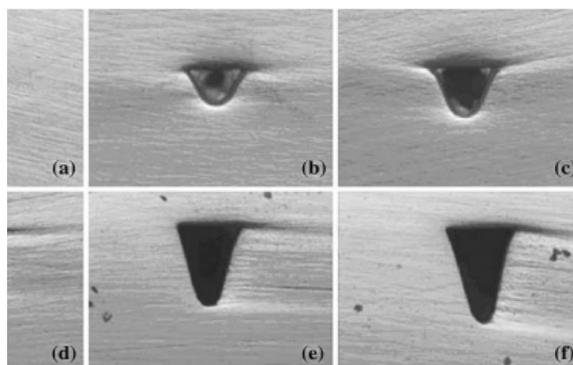
adhesive layer bonding for PMMA substrates [130]. Another common, inexpensive method for adhesive bonding is the use of lamination films as low as 40  $\mu\text{m}$  [129, 131], since most Commercial laminators are inexpensive and simple to use. The drawback to this system is intermediate adhesive layer mostly produces composite layer chip with inconsistent microchannel sidewalls and clogging of microchannels. Furthermore, the bonded surfaces tend to have different chemical, optical and mechanical properties than the bulk substrate. Although, an extensive range of UV-curable adhesives is accessible, they are typically derived from polyester or acrylate resins.



**Fig. 1.** Capillarity-mediated resin introduction of UV-curable adhesive [168]. Copyright Wiley-VCH Verlag GmbH & Co. KGaA, copied with permission.

## 2.2. Thermal Fusion Bonding

This direct technique involves the simultaneous application of pressure and heat on both substrates surfaces. This bonding process gives a moderately high bonding strength and is mostly applied to thermoplastic materials because the Substrates are heated to temperatures near or above the glass transition temperature ( $T_g$ ). Although, unrestrained temperatures and pressures application or use of materials with different  $T_g$  may lead to microchannel distortion and collapse. Hence, the use of a programmable hot press [130], [132-134] such as high throughput roller laminator [135] that can properly regulate temperature, pressure, and time is vital to attaining high bond strength while preventing deformation of the embedded microchannels due to bulk polymer flow. Using this method, consistent stability of channel cross-sections can be attained, as revealed in Fig. 2 that shows the case of laser micromachined channels in PMMA [136].



**Fig. 2.** Cross-sectional views of enclosed laser micromachined PMMA channels, with increasing depth from a–f, thermally bonded at 180 °C, well above  $T_g$ , using a low bonding pressure below 20 kPa [168]. Copyright IOP Publishing Ltd., reproduced with permission.

## 2.3. Solvent-Based Bonding

This technique is similar to adhesive indirect method because it that it requires a solvent between the merged surfaces. However, in this case the solvent used to bond the substrate together, temporarily soften and dissolves the material. Consequently, the surface molecules of the materials mix together to form a permanent bond as the solvent evaporates [153]. Solvent bonding of thermoplastics makes use of polymer solubility in designated solvent systems to achieve entanglement of polymer chains across the interface. As a result, the polymer chains become mobile and can freely diffuse across the solvated layer, leading to broad interweaving of chains between the surfaces to create exceptionally strong bonds [154]. PMMA substrates immersion in ethanol for at last 10 minutes before joining them together under pressure is a simple illustration is Solvent bonding that has been performed by this research group [139].

## 2.4. Localized Welding

It's a direct bonding technique that is commonly used on thermoplastic. It involves the use of ultrasonic energy to induce heating and tempering at the interface of the mating parts [140]. Another alternative method is the use of microwave energy to heat embedded metal films located between the desired bond surfaces. An advantage of this technique is selective use of energy to locally target specific regions or uniformly all mating interfaces for bonding [141]. There are commercially viable systems operating at 35 kHz [142] that can be efficiently used on thermoplastic polymers such as PMMA (Poly(methyl methacrylate) and PEEK (polyetheretherketone).

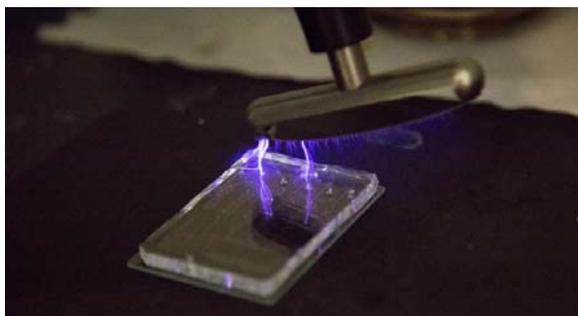
Synopsis of general bonding techniques is added in Table 3.

**Table 3.** Synopsis of general bonding techniques for microfluidic device [107].

Bonding Method	Bonding Strength	Bonding Quality	Process Complexity	Bonding Time	Cost	Advantage	Limitation	Suitable Material	References
Solvent bonding	High	Fair	Low	Low	Low	Simple, fast, low temperature, high bond strength, low cost	Soften polymer surface may collapse channel from un-optimized process	PMMA, PC, COC	[114-118]
Solvent Bonding with sacrificial Material	High	Good	High	Medium	Low	High bond strength, low cost, low channel collapse and clogging	Sacrificial material needed to be applied into channel before bonding and removed after bonding	PMMA	[119-120]
Localized welding	Medium	Fair	Medium-high	Medium	Medium	Low temperature, localized bonding	Energy director (ultrasonic welding) or metal layer (microwave welding) are required	PMMA, PEEK	[121-122]
Surface Treatment Bonding	Medium-high	Good	Medium	Medium	Medium-high	Low temperature bonding, low channel deformation	Surface chemistry changed after treatment	PMMA, PC, COC, PS, PET	[123-125]
Adhesive Printing Bonding	High	Fair	Medium-high	Short-medium	Low-medium	Low temperature, high bond strength, low channel clogging, controllable adhesive thickness	Scarification channel (contact printing) or printing mask (screen printing) required	PMMA, COC	[126-127]
Adhesive interstitial Bonding	High	Fair	Low	Short	Low	Low temperature, high bond strength, low channel clogging, controllable adhesive thickness	Soften polymer surface may collapse channel from un-optimized process	PMMA	[128-129]
PDMS-interface bonding	Medium	Fair	Medium	Long	Medium	Simple, fast, low temperature, high bond strength, low channel clogging, low cost	Sacrificial material need applied into channel before bonding and removed after bonding	PMMA	[108]
Lamination film bonding	Medium	Fair	Low	Short	Low	Low temperature, compatible with PDMS microfluidics	Energy director (ultrasonic welding) or metal layer (microwave welding) are required	PMMA, PC, PS, PET	[114], [130-131]
Thermal fusion bonding	Medium	Fair	Low	Long	Low-medium	Simple, fast, low cost, low temperature, no adhesive clogging	Surface chemistry changed after treatment	PMMA, PC, PS, Nylon, CO, PSU	[132-135]

## 2.5. Surface Treatment and Modification

This form of direct bonding technique that functions by increasing the surface energy of the substrates required to bond. Increased surface energy helps to improve the hydrophilic properties of mating surfaces. As a result, mechanical interlocking and inter-diffusion of polymer chains between the surfaces are enhanced [143]. The substrates are held together by the generation of electrostatic interactions, and also surfaces possessing high specific energy in the form of polar functional groups can create hydrogen or covalent bonds across the interface that are capable of producing bond strengths beyond the cohesive strength of the bulk polymer [144]. Similar to localized welding, selective region use of a mask can be used to apply surface treatment and modification to specific regions. For example, PDMS layer to be bonded is covered with a masking material during corona discharge treatment to protect areas from exposure to the corona plasma so that only the unprotected surfaces are activated. Subsequently, the activated surfaces are hydrophilic, with chemically active functional groups that binds to other activated surfaces, while the masked areas remain unbound [145-146]. This example is an illustration of O<sub>2</sub> plasma surface treatment done by the aid of corona discharge (Fig. 3).



**Fig. 3.** Corona discharge used to bond surfaces of PDMS to glass.

Corona discharge used for bonding is a process by which an electrical discharge occurs between an electrically charged conductor (electrode) and the surface of a substrate. This occurrence is as a result of potential gradient (electric field) and ionization of the neutral media fluid, typically air [147]. This fluid ionization process creates a region of plasma around the electrode as free electrons randomly accelerate across the air gap in the presence of a high voltage discharge. Subsequently, when a substrate surface is positioned in the discharge path, high energy electrons create free radicals by colliding with the surface to breakup their molecular bonds. These free radicals form various chemical functional groups [148-149] required for effectively increasing surface energy and enhancing chemical bonding to another activated surface, in the presence of oxygen

(oxidational reaction). Examples of functional groups include carbonyl (-C=O-). Carboxyl (HOOC-), hydroperoxide (HOO-) and hydroxyl (HO-) groups [149-105].

Ultraviolet light (UV), is a simpler alternative to plasmas for the enhancement of substrate surface energy. The Exposure of UV light to polymer substrates especially thermoplastics results in photodegradation, which is the primary mechanism creates photo-oxidation and breakup of polymer chains on the surface [150]. Typically, light exposure within the range of 300–400 nm is usually sufficient to break chemical bonds within most thermoplastics [151-152].

## 3. Prototype Fabrication Technology

The need to manufacture POCT devices at relatively cheap cost brought about rapid development microfabrication technology in the medical field. The earlier years of microfluidics devices were predominantly produced with techniques borrowed from the microelectronics field, and they predominantly involved materials like glass, quartz or silicon. However, the advent of new technological processes brought into focus the demand for devices which are disposable and inexpensive.

Contemporary techniques can be distinguished by their individual protocols employed to establish efficient channel network or fluid circuit in the chip. The chip functionalities, are largely defined by microchannel aspect ratio, with channel dimensions as low 0.1  $\mu\text{m}$  to as large as 500  $\mu\text{m}$ . As a result choice of fabrication methods are tied to the anticipated channel dimensions on cost and production time. They can be divided into two areas: material depositing techniques and material removing technique.

### 3.1. Material Depositing Technology

This represent the successive build of bulk material on a substrate or a Standalone structure which can be used directly or as a mould for replication of microfluidic components. Parts produced can be used directly or bonded to achieve expected functionality. While the case of replication involves indirect use of fabricated parts to create intended components for utilization. In layer-to-layer manufacturing a part is broken down into multi slices that are then created and coupled by means of solvent or heat supported lamination or bonding processes. The materials used are usually wax, resin or powder. A good example of this techniques is 3D printing.

### 3.2. 3D Printing

3D printing that utilize a layering accretion system to build solid structures from either liquid

resin or powder from a digital file. This technology offers a broad range of methods to synthesize solid structures of various shapes or geometry that differ in physical characteristics with respect to the method of production.

These methods includes stereolithography (vat Photopolymerisation), ink jetting, binder Jetting, Material Extrusion and Powder Bed.

### **3.2.1. Stereolithography**

Stereolithography (STL) is a conventional additive layer-on-layer manufacturing technique. STL is one of the most significant rapid prototyping methods in the microfluidic research industry today. It can be used to create very fine structures and, more importantly, allows for fast turnaround of functional prototypes used directly or replication molds. The basic process is called Vat Photopolymerization [175], it involves consecutive 'printing' thin layers of a curable material, e.g., a UV curable material, cumulatively on top of another by the use of UV Laser beam. The three-dimensional model (3D CAD design) is divided into thin micro multiple layers before light exposure. Upon exposure to UV light, the surface of the liquid resin solidifies. This hardening process is responsible for forming successive individual layers of the anticipated 3D object and is carried out repeatedly till 3D object is formed [176].

The Parts produced, based on this technique do have the considerable mechanical toughness and are capable of high detail definition. However, they do have some disadvantages such as post production that involves immersion in a chemical bath to eradicate unwanted resin before being cured in an ultraviolet oven. Likewise, the support structures which are interminably present can be difficult and time-consuming to remove. Their dependency on UV light has gradually being reduced as recent improvement of photoinitiators, have afforded several options in the choice of light not restricted to UV. As a result, extensive range of high-intensity light sources of differing visible wavelengths can be used as a choice for polymerization [177-178].

### **3.2.2. 3D Inkjet Printing**

Inkjet 3D printing process is similar to regular inkjet paper printer but in this case light curable resins and wax instead of inks. In this combination, the wax is expected to create spatially constrained volumes which are to be filled with the light curable resins. The sequence of layer building involves an array of nozzles that create droplets of heated low viscous wax that instantaneously form cavities which are subsequently spotted with resin before cured by light exposure.

Similar to STL this system can be used for an extensive range of microfluidic fabrications involving

mold replications. Although their final product finish is not as detailed as STL; they are still relatively close in comparison. Furthermore, the print mixture of UV curable acrylic resins and waxes makes easy post cleaning process because the waxes serve as supporting materials that can be removed easily. The foremost downside of inkjet printing is that most parts produced from this technique cannot be used directly because due to low chemical or biological compatibility [121].

### **3.2.3. Binder Jetting**

The technology was originally developed at the Massachusetts Institute of Technology in 1993. The technological process of layering involves the use of glue applied through jet nozzles to bind together powder based particles spread in equal layers using a slider that guarantees a smooth and even surface. The building space is typically a platform onto which a thin layer of powder is spread cumulatively to form the shape of a programmed 3D object. After the consecutive accumulation of layers, the finished part is typically tempered to allow full curing of the glue. Subsequently, the non-bound powder particles are then cleaned off.

This system pales in comparison to STL or 3Dinkjet in product finish but what it lacks in finishing it makes up in cost and faster turnaround. Conversely, this technique does have a major drawback: the dominant chemical and physical properties of the part created is defined by the glue used. In addition, parts created by this process can't be transparent because of the solid particles combination. Likewise, inconsistent binding of particles can result in porosity which makes it highly unsuitable for direct microfluidic use because of potential leakages. Again, this method is mostly suitable for mould creation for microfluidic chip models of bigger aspect ratio because the difficulty of removing powder from long and narrow channels.

### **3.2.4. Material Extrusion**

The Fused deposition modeling (FDM) technology is a commonly used material extrusion technique. The process involves a precise control of heated material through a plastic filament or coiled metal wire. Layers are built by two nozzles; one for the primary material and another for the support structure. The primary nozzle extrudes molten material forcefully out in both horizontal and vertical directions before hardening. The material mostly used are Acrylonitrile Butadiene Styrene (ABS) and Polylactic acid (PLA). Concurrently, secondary nozzle also typically ejects water soluble material for internal structures while low mechanical strength structures for external support. FDM has a unique advantage from other techniques, due to its ability to create multi-materials components without the need

of specific polymer modifiers [179]. Thus, materials with different chemical or physical properties can be applied (including stiffness and color) subsequently. Acrylonitrile butadiene styrene (ABS) is a commonly used material in FDM while conventional polymers such as PC, PCL, PP or PS can be used as well in this process. The main weakness of FDM is the inconsistent definitions of the part geometrical structure as a result of the layer deposition characteristics that tend to mirror vivid shapes of the cylindrical wire used for layer formation [269]. As a result, the final microchannel surfaces are rough, and sidewall shapes are skewed. This disadvantage disqualifies direct microfluidic use because the skewed channels can cause flow obstruction, leakages and most especially surface binding issues. Still, FDM can be suitable for mold replication because of fast turnaround, low cost of fabrication and no post curing.

### **3.2.5. Powder Bed**

This process is similar to binder jetting but in this case, a high-powered laser is used to fuse small particles plastic, metal, ceramic or glass powders into a concise bulk of the anticipated 3D object. Unlike binder jetting, the chemical and biological compatibility of the created parts are defined only by the bulk material properties. The most commonly used technique for this process is Selective laser sintering (SLS) which builds up layers by using a laser beam to scan selectively across the surface of the powder bed. After each cross-section is scanned, the fused powder mass bed is lowered by one layer thickness before a new layer is applied on top and the routine is repeated until the object is completed. In SLS there is no requirement for support structure since all untouched powder remains becomes support for the sintered ones.

As of yet this technique suffers major limitations in either direct use or indirect (mould replication) use in microfluidic research because the created parts are porous thus leading to mechanical toughness and surface finishing impairment.

### **3.2.6. Lithography**

Lithography is a hybrid of both material removing and deposition technology. It is essential to note that lithography can be defined regarding direct use only. In the broad spectrum of prototyping, techniques lithography leans towards material deposition, although it requires material removal techniques as a complementary process to achieve the anticipated functioning POCT chip. The rudimentary process behind is selective lithography imprinting, which involves creating patterns on specific areas while simultaneously protecting areas not preferred untouched. For instance, ink can be used to create patterns on a material while the areas that are expected to be untouched are covered with wax.

Good examples of these techniques that can be utilized for microfluidics fabrication are optical and X-ray lithography.

### **3.2.7. Optical Lithography**

Optical lithography makes use of UV light to transfer geometric patterns on top of sensitive materials that are known as photoresist on the surface of a substrate. Commonly used substrate and photoresist are silicon wafer and SU-8. The process starts with the deposition of silicon dioxide ( $\text{SiO}_2$ ) which serves as a barrier layer on the surface of the wafer. Subsequently, a technique is known as spin coating [180-181] is used to build the required height in micrometers by uniform layer on layer deposition on the wafer surface. Irradiation is then applied through a glass photomask that can cause the exposed resist to either be more soluble (positive resist) or less soluble (negative resist). For positive resists, the dissolution by solubility that occurs due to light exposure is washed away by the developer solvent to leave precise openings surrounded by walls of resist untouched. The exact opposite is the case for negative resists as exposure to light induces polymerization that causes the resist to be insoluble to the developer solution. Whereas the unexposed area are then removed by the developer solution.

The main advantage of this technique above others is the closure of micro-channels which is inclusive in the fabrication method without any additional bonding process. Micro-channel development depends on several key factors which include resisting material, spin rotational speed, the power of exposure and tilting angle of the substrate. On the other hand channel, the closure can be achieved after the initial light exposure and developer treatment is carried out, a second SU-8 layer is spun on top and processed similarly. As well, the use of SU-8 can also allow on-chip integration to other SU-8 created functional components, like micropumps, microvalves, and complex microfluidic networks [182]. The recent improvement in technology has afforded cheaper, and faster alternative using dry film resist (DFR) [183-184]. DFR offers numerous advantages over liquid resist (SU8) such as good adaptability, exceptional adhesion to any substrate, decent flatness, no requirement of liquid handling, even resist distribution, low energy exposure, low cost and short processing time. However, the main challenge of this method is the setting up cost which is relatively very high in comparison to other techniques even though DFR have cheaper to setup than SU-8. Furthermore, SU-8 are predisposed to large internal stress and once developed; they are very difficult to be removed from structures. Likewise, both liquid and a DFR require a uniform flat substrate to create precise structures; they also are not effective in create non-flat surface structures, and require an extremely clean room environment for its protocols.

### **3.2.8. X-ray Lithography**

Lately, X-ray lithography has been adapted [185-187] for fabricating polymer microchannels using PMMA as substrate. PMMA is a suitable material for this process because of its high sensitivity to X-ray absorption (mild X-rays of 0.7-0.8 mm) and degradation. This technique is similar to the positive resist technique of optical lithography. But in this case, the photomask that bears the geometrical patterns is made of gold. Gold is a typical X-ray absorber because of its high atomic number, and the mask thickness depends on of the intensity of the exposure. For example, the gold mask must be approximately 5 to 10 micrometers thick to absorb x-rays with energy in the range of 5 keV to provide corresponding depth into PMMA of several hundred micrometers [188]. As the thick gold layer absorbs X-rays, the sections that are transparent to the X-rays are degraded. On the other hand, the photoresist which is PMMA can be spun as one single layer, multiple layers or joined as a pre-cast commercial sheet. The sheet is joined to the substrate by the liquid monomer, MMA. After the exposure, the degradation of PMMA into soluble oligomer [189] before they are dissolved in a developing solvent comes as a result of X-ray induced scission reactions.

This technique yield better high aspect ratio structures than photolithography because X-ray operates at a much shorter wavelength than UV light, even Deep UV (DUV) [190] light and also provide increased lateral resolution. However their setup cost goes into millions of dollars, and operating cost can run into hundreds of dollars per hour just to recuperate the actual operating expenses. Nevertheless, subsequent duplicates PMMA molds can be made from the master synchrotron made mold reduce cost by injection molding or hot embossing. This method is mostly suited from replication, not direct use.

### **3.3. Material Removing Technology**

Unlike material depositing techniques, material removing techniques creates structures by locally removing material from designated parts of a bulk. In microfluidics techniques such as laser ablation, micromilling or etching are commonly used. These methods typically creates negative spaces that form the microchannels and fluidic elements in substrates. However they are generally not suitable when cost of the substrate is a major concern.

#### **3.3.1. Etching**

This technology is one of the earliest fabrication method used in microelectronics or MEMS involving silicon and glass. Likewise, they have mostly being

used as a complementary process in techniques as optical lithography and micromachining. Due to current trend glass, microfluidics components seems to be the preferred choice in the POCT field due to its physical characteristics of transparency. Etching techniques are categorized either as dry or wet etching. When the material is removed from it can do by either process it can either be isotropically (uniformly in all directions) or anisotropic etching (constant surface area and uniformity in depth). The major difference between the two processes is the material removal rate which is faster in wet-etching and can be subjected to varying temperature or the concentration of the wetting agent. Though, both require mask similar to optical lithography so only unmasked areas will be touched. In dry etching, the removal process is done by physical, chemical or both means. Physical dry etching utilizes plasma that generates bombarding ions, electrons or photons with high kinetic energy to knock out the atoms from the substrate surface, which in turns results in material disintegration by evaporation. While, the case of chemical dry etching don't require actual liquid etchants but instead gas etchant such as tetrafluoromethane (CH<sub>4</sub>), sulfur hexafluoride (SF<sub>6</sub>), nitrogen trifluoride (NF<sub>3</sub>), chlorine gas (Cl<sub>2</sub>), or fluorine (F<sub>2</sub>) [191] to cause surface ablation. A commonly known combination (physical and chemical) is called reactive ion etching. This process is the most extensively used dry etching technic because it's faster and able to achieved better resolution than both the physical and chemical results. The method of operation involves dissociation of enchanting molecules to more reactive species by high energy collision from plasma ionization reaction.

On the other hand, wet etching involves exposing the substrates to corrosive solvents in liquid form. As the liquid etchant diffuses across the exposed surfaces, a reduction-oxidation reaction occurs between the liquid-solid interfaces causing degradation. Furthermore, the rate degradation determines is determined by the concentration of the etchant. Isotropic wet etching uses a combination of hydrofluoric acid, nitric acid, and acetic acid (HNA) as etchant solvent for silicon. While, potassium hydroxide (KOH), ethylenediamine pyrocatechol (EDP), or tetramethylammonium hydroxide (TMAH) are some of the anisotropic wet etching agents for silicon [192]. The major advantages dry etching is anisotropic etch profile is easily attainable, etchant consumption is relatively small. Whereas, wet etching requires simple equipment and possess high substrate selectivity. For the disadvantages, dry etching requires complex equipment and protocols, while their substrate material selectivity is very low. The major setbacks of wet etching are relatively high cost of etchant and inconsistent precision (prone to undercutting) of small geometries [193-194]. Overall, it is possible to use this technique for replication mould or direct use in microfluidic chips fabrication.

### **3.3.2. Laser Ablation**

This micromachining process involves using a powerful laser to shape or create geometric structures on a substrate. Just as lithography and etching techniques discussed ablation may be achieved by exposure through a mask. The defining difference between the substrate and mask is the significant absorption at the laser wavelength. For the mask, they are expected to have very low absorption, e.g. most metals. A good example of a commonly used substrate is PMMA due to its significant absorption of the emission wavelength of the laser (i.e. 427 °C for PMMA) [195]. Alternatively, direct-write maskless systems can still be used to create channels and other microfluidic structures. In this process, the laser is held at a constant position while the platform that bears the substrate is moveable. This technique has a better turnaround because the design of the microchannel network can be changed quickly during the prototyping process instead of time spent designing new masks. While the drawback of this method is the inability to mass produce parts since they are made in a sequential manner.

In general, the shape develops by laser ablation are usually square or rectangular with straight edges. Moreover, laser-ablated channels have far worse surface roughness than most material removing techniques. The degree of roughness is highly reliant on the absorption of the polymer at the excimer wavelength. While, the depth of laser-ablated channels is dependent on many parameters including polymer absorption, laser power, pulse rate, and some passes made across the channel. There are varieties of commercially available plastics such as polycarbonate, polystyrene, cellulose acetate, and poly(ethylene terephthalate) [170, 196-197] that can be used to fabricated microchannels using ArF excimer laser (193 nm) [198].

### **3.3.3. Micromilling**

Micromilling process involves micro-cutting that is characterized by the mechanical interaction of a fast spinning piercing tool that causes splintering within specifically defined paths on the substrate. The residue of this process is usually in the form of chips [199] that can be easily blown or washed off. This method is mostly suited to mold replication in microfluidics, and the type of material general used as substrate are metals (e.g. aluminum). Although polymers can also be subjected to this process, they are highly selective due to their comparable mechanical strength to metals. PMMA is a good example of commonly used polymers because of its good mechanical strength, thermal resistance, and dimensional stability. Furthermore, PMMA optical transparency also provides a major advantage. The capability of producing high-quality microchannels and other geometric structures are determined by the material, diameter and sharpness of the cutting tools.

The main cutting tools in this miniaturization process are cemented carbide and diamond. Both tools achievable minimum width of the microchannels is proportional to the diameter of the tool. There are commercially available carbide tools down to the size of 5  $\mu\text{m}$  while diamond is within the Range of 100  $\mu\text{m}$ . However, tools below 100  $\mu\text{m}$  are prone to unpredictable failures. In the case of tool sharpness, diamond mills are within the range of 50 nm and are capable of surface roughness Ra 10 nm with no burrs (channel edge roughness). Whereas, carbide mills have a sharpness around 1  $\mu\text{m}$  to 10  $\mu\text{m}$  [200], that can create surface roughness of about 0.1  $\mu\text{m}$  to 0.3  $\mu\text{m}$  Ra [201] with considerable burrs.

The major shortcoming of micromilling is the difficulty in defining small geometric structures consistently due to excessive tool failure. Furthermore, they do have expensive setup cost but are relatively cheaper in comparison to lithography. On the bright side, Micromilling is a capable and cost-effective technique to fabricate PMMA microfluidics for research purposes.

### **3.3.4. Micro Electrical Discharge Machining**

Micro Electrical Discharge Machining (EDM) is quite similar with the principals of macro Electrical Discharge Machining the only difference is the plasma channel diameter. Micro-scale EDM is a thermal process that utilizes electrical discharges to erode electrically conductive materials. Since the materials only applicable are metals, this easily categorizes this method as means for mold making. This process involves two electrodes that are separated by a dielectric medium, then brought together to a specific threshold were the dielectric medium breaks down and becomes conductive. As a result, sparks will be generated between the electrodes that creates a successive surge of thermal energy. When this thermal energy is released, it causes the material surface to melt and evaporate rapidly, creating voids. The precise control of the energy magnitude regarding voltage and current can help create micro features on any electrically conductive material. Since  $\mu\text{EDM}$  is a no-contact and no-force process in comparison to micromilling they can easily be used to cut micro features of complex shapes and thin walled microchannels without distortion. Moreover, the  $\mu\text{EDM}$  process leaves no burrs. The major drawbacks are the use of only conductive materials, i.e., (insulators) are out of the process. Moreover, setup cost is more expensive than conventional micromilling.

## **4. Prototype Replication Technology**

This technological process is employed for the sole purpose of replicating parts and components that are integral to the entire POCT chip formation at a mass production level. Commercial viability is also

key to this process, as a low cost at high quality improves marketability. Consequently, this is targeted towards end users, but some of its methods can also be utilized in research prototyping. A typical process involves selection of precision fabrication technique to create a master mould that bears the intended design to be replicated through a specific process to several parts.

#### **4.1. Injection Moulding**

In this replication method, wet or dry etching techniques are employed to create structures with higher aspect ratios [202] and precise geometrical features on a silicon substrate. Subsequently, nickel electroformed [202] is the process used to produce the metal master mold by electroplating a layer of metal, with a thickness within the range of few micrometers to a few millimeters. Metal masters are a lot stronger and longer lasting than masters made of silicon, glass or polymers. They can be utilized to yield hundreds of thousands of injection molded parts with features microfluidic elements. The replication process involves the nickel electroformed being mounted onto a mold insert and the polymer of choice is melted to a viscous liquid when pushed by a mechanical screw through a heated chamber. Afterward, the liquid polymer is injected at high pressure into the mounted mold (with nickel electroforming), and as contact is made with the mold walls, the heated polymers start to cool down, resulting in well-defined solid features [203]. Injection molding technique is very versatile and almost any plastic part, or component can be made efficiently. PMMA [204] and PC [205] are good examples of polymers used in this replication process. The major advantage of this technique is accuracy; it can be used to produce channel sizes ranging from 10  $\mu\text{m}$  to few hundred micrometers. Their major Limitation is that they are not cost effective for research prototyping since few copies are required with a frequent change of designs.

#### **4.2. Hot Embossing**

This method shares a similar process to injection molding in the case of metal master mold preparation. However, this technique involves the use of a hydraulic press to imprint the master mould forcefully on a polymer material after it has been softening to a temperature close to the  $T_g$ . The stamp with the mold design is applied at low pressure for a period less than 10 minutes on the plastic. As a result plastic, microchannel features are the exact mirror of the metal stamp. Alternatively, this same process can still be done in plastic at room temperature, but high pressures. Though the turnaround time is a lot shorter, the product finishing is much more dependent on numerous constraints including imprinting pressure, imprinting time and properties of

the plastic itself [205]. Moreover, the lifespan of room temperature imprinting is a lot shorter than at elevated temperature.

Hot embossing or room temperature imprinting can be successive done on several types of plastic with excellent device-to-device reproducibility. Good examples of plastics include polystyrene (PS) [206], polyethylene tetra phthalate glycol (PETG) [207], polymethylmethacrylate (PMMA) [208], polyvinylchloride (PVC), and polycarbonate [209]. Just like injection molding their downside is the setup cost and lack of flexibility in design altering needed for prototyping research.

#### **4.3. Soft Lithography**

Soft lithography is a widely used rapid and efficient way to create microfluidic prototypes. This method is a very cost effective and is used extensively for research for research purposes. As with all other techniques described thus far, a positive relief master may be needed, but not necessary in silicon. As for this technique, since its research inclined the turnaround time is highly dependent on the fabrication method of making the master mold. As of recent 3D printing techniques have been useful in fulfilling this requirement because of the flexibility involved in design changes endemic in rapid prototyping. In the case of material utilized, an elastomeric polymer that is liquid at room temperature is required to be cast onto the master mold and allowed to cure at a high temperature. Subsequently, the cured material with the micropatterns is bonded to another substrate more likely glass, before they are functional. A commonly used material for this process is PDMS because of its favorable mechanical and optical properties. PDMS is a mixture ratio of a prepolymer and curing agent. A standard mix ratio is 10:1 (i.e. 10 g of prepolymer to 1g of curing agent) [77]. As a result, the mechanical properties of PDMS can be narrowly altered by either increasing the prepolymer to reduce elastic modulus or increasing curing agent to increase elastic modulus. The curing process of PDMS can occur slowly at room temperature or speedily at a slightly elevated temperature (generally 40–70°C for PDMS) before they are peeled off the mold. Polyurethane elastomer is a very good alternative to PDMS as it has better comparative mechanical strength [210] with optical transparency. However, the protocols involved in casting are very stringent and do have potential health [211] concerns.

The major drawback in soft lithography is the design limitation since most moulds are created as either positive or negative the outcome of the cast is a 2.5 Dimensional (2.5-D) object that requires another layer substrate (glass or similar material) to complete it. Although, the fabrication of 3-D is not somewhat impossible but will require several designs of molds, that are individually representative of different layers in a multi-layer three-dimensional structure [212].

## 5. Conclusions

In this paper, material properties such as mechanical resilience, transparency and high-temperature tolerance and biocompatibility form the major characteristics needed in POCT substrates. Amongst the various material discussed polymers as substrate have shown better significance due to their wide range of material characteristics suitable for microfluidic applications. Good examples are the combination of both good optical and thermal characteristics needed in primary chip functions such as DNA amplification and detection. PDMS, PMMA, PC and COC tend to be most widely used polymers due to their low cost, ease of fabrication and market availability. However, other materials that pale in comparison to polymers such as metals, silicon, etc. which don't account for the bulk parts of the POCT chip, do contribute to other microfluidic elements creation or enhancement. For instance, silicon can be used for electromechanical components such as electrostatic diaphragms for valves or pumps. While gold can be used as alternate means of optical high-sensitivity detection by in microfluidic channels by Resonant light scattering spectroscopy.

On the other hand, fabrication techniques mainly revolve around setup cost, production cost, surface roughness, the simplicity of operation and aspect ratio definition. Of all the above attributes mentioned, none of the fabrication technique discussed offers a total solution. Moreover, it can be deduced that as the surface finish and aspect ratio improves there is a significant correspondence in the product and setup cost. Besides, prevalent technology makes some of these techniques not yet appropriate for POCT device creation because of the unsatisfactory surface finishing or the limited choice of materials that can be processed with their respective protocols. Nonetheless, 3D print offers a reasonable solution in academic or research environment as a result of the recent improvement and economic availability of printers in the marketplace. While for the commercial aspect, hot embossing, and injection moulding are the still the best available option as of yet.

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