Plastic fantastic?

Andrew de Mello reviews the potentials of polymers and plastics as substrate materials in microfluidic applications

Without doubt, the conceptualization and development of the miniaturized total chemical analysis system (μTAS) over the past decade has revolutionized the way scientists can address a variety of complex chemical and biological problems. Since Andreas Manz and Michael Widmer presented their visionary concept in 1990[1] the evolution of the field has occurred at a truly exponential rate. Today, Lab-on-a-Chip technologies are routinely used in a wide variety of application areas including separation science, protein analysis, process control, environmental monitoring, chemical synthesis, DNA amplification, immunoassays, DNA sequencing, and cell manipulations.[2]

The rapid acceptance of miniaturized systems for analytical and measurement applications has been motivated by a number of reasons. At a fundamental scientific level, miniaturized analysis systems exhibit clear advantages when compared to their conventional (macroscale) counterparts. These include improved efficiency with respect to sample size, response times, analytical performance, process control and throughput. Furthermore, the fabrication methods necessary to create system features on the micron scale had been defined, developed and refined within the microelectronics industry for over almost half a century. This foundation of technological expertise in bulk and surface micromachining of silicon and silicon-compatible materials very simply meant that the creation of microfluidic chip devices (containing elements such as flow-manifolds, valves, reactors, electrodes, detectors and filters) was achieved in a relatively short timescale.

In the beginning

A cursory glance through the literature in the early 1990′s reveals that almost all early microfluidic systems were constructed from glasses, quartz or silicon as the substrate material. This is not surprising since standard photolithography and wet-etching techniques could be used to efficiently structure all these materials to produce microchannel networks. Much of the early work in the field focussed on transferring separation methods to planar chip formats, and in particular the development of electrophoretic separation technology.[3,4] Although, silicon-based CE chips have been reported, the conductivity of silicon proved problematic when applying high voltages necessary for the generation of electroosmotic flow (EOF).[5,6] Consequently, the vast majority of early microfluidic systems were sculpted from glassy materials. Glasses possess beneficial properties such as well-defined surface chemistries, superior optical characteristics and good electroosmotic properties. However, machining these materials presents a number of problematic issues that may ultimately hinder their widespread use in commercial applications:

Cost of substrate materials

Although many microfluidic chips have small footprints (~1 cm^2) larger fluidic devices (~100 cm^2) may be necessary for screening or high-throughput applications. This means that often the cost of the raw substrate material is a significant factor in mass-production (glasses range in cost from approximately \$500–4000 per m^2).[7] Although, integration of multiple devices onto a single substrate can dramatically reduce device cost, performance issues normally limit minimum feature sizes and thus the number of devices per unit area.

Fabrication infrastructure

Fabrication of planar glass devices is a serial operation (in which substrates are cleaned, lithographically patterned and etched). Although each process is well defined, fabrication is often a time-consuming and expensive process (in part due to costs associated with the establishment and maintenance of cleanroom facilities).

Feature aspect ratios

The isotropic nature of wet-etching processes generally yield channels with sloping walls and of relatively low aspect ratios (the ratio of feature height to width). For some applications, this type of channel shape is adequate, but for many others (*e.g.* distributive fluidic mixing) deep narrow channels are beneficial. Fabrication of high aspect ratio features in glass is a non-trivial process and requires access to more specialist fabrication facilities.

Bonding of glass devices

To create usable fluidic structures etched substrates are normally thermally bonded to a coverplate made from a similar material (at temperatures in excess of 400 °C). This process is serial in nature and often time-consuming.

With this brief analysis in mind, it is clear that if microfluidic devices are to be mass-produced for a wide variety of real-world applications, alternate substrate materials and fabrication methods must be adopted. Ideal materials should:

(i) Be available in a pure form at low-cost.

(ii) Possess appropriate chemical, thermal and electrical properties for the desired application.

(iii) Be compatible with chemical and biological reagents.

(iv) Possess superior optical properties to allow for facile monitoring during analysis.

(v) Be easily machinable and applicable to mass replication technologies.

(vi) Allow facile bonding and encapsulation of the structured substrate.

(vii) Provide for a variety of surface properties.

Although, no single material offers a perfect solution to all these constraints, polymers and plastics represent a broad class of materials that perhaps best qualify this wish list. They provide for a wide range of material properties, are available in pure forms at low cost, and can be machined and replicated in a variety of manners. Not surprisingly, these qualities have provoked enormous interest in the development of plastic microfluidic chips devices for a wide variety of analytical and commercial ends.[8,9] This mini-review aims to assess the potentials of plastic devices for microfluidic applications and to describe some of the key advances over the past few years.

Materials

At a basic level, polymers are macromolecular substances with a high molecular mass. They are formed *via* polymerization reactions whereby

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monomer units react to form either linear chains or a three-dimensional network of polymer chains. Homopolymers are formed when only one monomer is employed and copolymers (often with superior properties) are obtained by using a variety of monomer units. Polymers can be broadly classified according to their properties (and thus underlying molecular structure) into three groups: thermoplastics (crystalline or non-crystalline), elastomers (or rubbers) and thermosets (or duraplastics). Thermoplastics are linear or branched polymers which can be melted upon application of heat (*e.g.* polystyrene (PS) and polyethylene (PE)). Elastomers are weakly cross-linked polymers that can be easily stretched to high extensions, but will adopt their original state when the stress is released (*e.g.* poly(dimethylsiloxane or PDMS). Finally, thermosets are heavily cross-linked polymers that are normally rigid, brittle and intractable (*e.g.* Bakelite).

Due to the wide range in physical and chemical properties of polymers and plastics (polymers containing specific additives) there should in theory be an ideal polymer for any specific microfluidic application. Nevertheless, this also means that a variety of fabrication methods are needed to allow efficient machining of very different materials.

Fabrication

The diversity of methods available for machining polymeric chips can be broadly separated into *direct fabrication* methods and *replication* methods. In direct methods (such as laser ablation, reactive ion etching and mechanical milling) individual polymer surfaces are structured to form system features. Replication methods (such as injection molding, hot-embossing, compression molding and soft-lithography), on the other hand, involve the use of a precision template or master from which many identical polymer microstructures can be made. A very brief summary of the most common techniques will now be given. More extensive details of fabrication methods can be found in excellent review articles by Holger Becker[7,8] and Steven Soper.[10]

Injection molding

Injection molding techniques are hugely versatile and can be used to fabricate a wide variety of structures in thermoplastic materials. Injection molding is an excellent tool for plastic replication due to its good dimension control, short cycle time (several seconds), and high productivity. Briefly, the polymer of choice is melted and then injected under high pressure into an evacuated cavity containing a precision master mold. The cavity is maintained at a temperature close to the melting point of the polymer to allow efficient fluid flow into all parts of the mold. The cavity is then cooled and the microstructured part ejected. Fig. 1 illustrates an injection molded acrylic substrate for use in electrophoretic applications.[11] It should be noted that he quality of surface features within the fabricated device is almost completely dependent on the quality and precision of the master template.

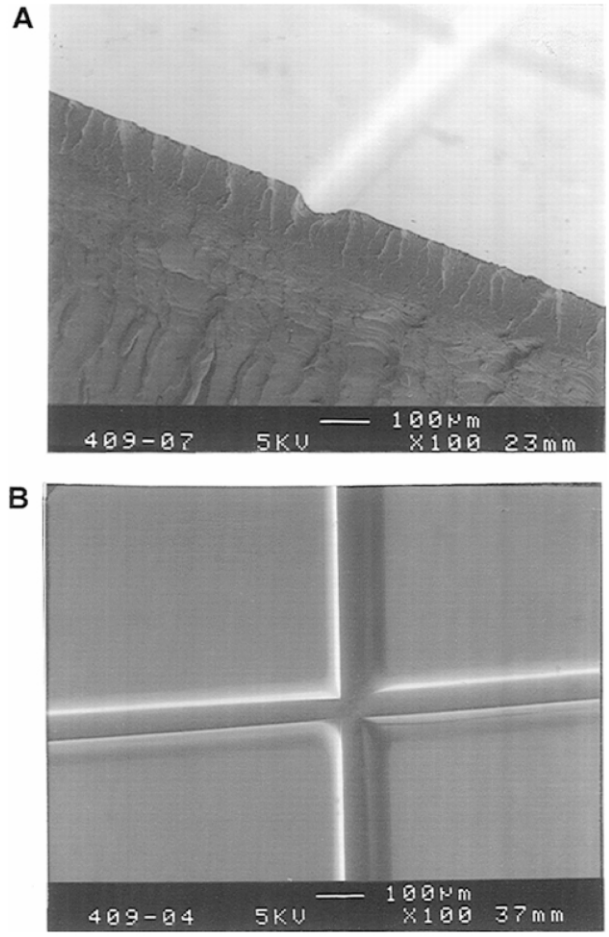

Fig. 1 Electron micrographs of (A) an unsealed microchannel in an acrylic substrate and (B) a view of the injection region on an acrylic CE chip. Reproduced from ref. 11 with permission.

Imprinting and hot embossing

Imprinting methods provide an efficient way to microstructure polymer surfaces. At the simplest level micron diameter chrome wires can be pressed into the polymer surface and heated to temperatures slightly below the glass temperature (T_g). Removal of the wire after heating yields microchannels with widths down to approximately 10 microns.[12] The primary disadvantage of this approach is a lack of reproducibility when fabricating multiple structures. An improvement to this approach is through the use of a silicon machined negative template (made using conventional lithographic procedures).[12] In a similar fashion, the template is simply pressed into the substrate material and then heated to a temperature above the polymer's T_g. Polymer hot embossing is a novel and cost effective method for the fabrication of micro- and nano-structures on large surfaces. A master template (commonly made using silicon micromachining or LIGA techniques) and a planar polymer substrate are heated separately under vacuum to a temperature close to the polymer's T_g. The template is then brought into contact with the substrate and embossed (or pressed) using a constant force. The two are then cooled to just below the T_g and pulled apart. Since many different plastics may be hot-embossed, a large number of microfluidic devices made using this method have been reported.[12–14]

Soft lithography

Soft lithography has become highly popular over the past five years, offering a

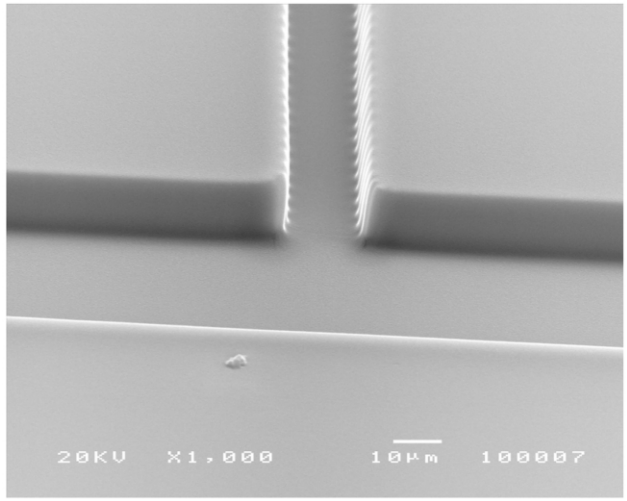

Fig. 2 Electron micrograph of 15 µm width channels created by molding of PDMS against a photolithographic master. Courtesy of Dr A. J. de Mello.

rapid, flexible and low-cost route to the creation of micro-sized features on planar substrates. Soft lithographic methods describe the molding of elastomeric polymers using master templates.[15,16] Elastomeric siloxane polymers such as PDMS are easily molded, optically transparent (well into the UV), durable, cheap, chemically inert, non-toxic and stable over wide temperature ranges. PDMS can be cast against a positive relief template to form microfluidic structures with high aspect ratios by simply pouring a mixture of the elastomer precursor and a curing agent over a template (Fig. 2). After curing the structured polymer is peeled away from the template and an enclosed fluidic structure created by contacting the elastomer with a planar surface. The seal between the two surfaces need not be permanent (facilitating fluidic cleaning and removal of blockages), although treatment of surfaces with an oxygen plasma allows siloxanes to be irreversibly bound to a variety of substrate materials. Importantly, templates can be made by a number of methods including silicon micromachining,[17] lithographic patterning of photoresists,[18] high-resolution printing,[19] photocopying[20] and solid object printing.[21] Furthermore, once a master has been structured all soft-lithographic processing can be performed under normal laboratory conditions.

Laser ablation

Laser ablation involves the use of high-power laser pulses to break chemical bonds in the polymer chain and eject degraded polymer fragments from the ablation volume (*via* laser induced shock waves). Common sources for laser ablation include KrF and ArF excimer lasers operating in the UV at frequencies between 10–10^4 Hz. At powers of a few hundred mJ per pulse each pulse can ablate approximately 0.5 µm of polymer. Furthermore, since many polymeric materials exhibit significant absorption in the UV a wide variety of polymers may be structured this way, including PS, PC, PMMA, nitrocellulose and polyethyleneterephthalate (PET).[22–24] As an example, Fig. 3 illustrates a network of curved microchannels ablated in a planar polycarbonate surface. Substrates may be machined using a direct-write (maskless) process, or through a lithographic mask that defines the area to be patterned. Although direct-write processing is advantageous during the prototyping process, structuring is performed in a sequential manner, limiting its usefulness in mass production of commercial devices. An attractive feature of laser ablation is the ability to modify surface chemistries during the ablation process (due to the formation of reactive species). Incorporation of these products on channel walls can yield functionalities dramatically different to those of the bulk material.[24]

X-ray lithography

Some polymers exhibit strong absorption bands in the X-ray region of the electromagnetic spectrum and are therefore susceptible to photochemically induced degradation. Most notably, PMMA has a high extinction coefficient between 7 and 8 Å and can therefore be structured using soft X-ray beams.[25,26] X-ray masks are commonly made from Kapton (transparent to X-rays) and gold, and are fabricated using conventional optical lithography. The polymer is then irradiated through the mask, and exposed regions removed using a variety of developing solutions. This process, although complex, can generate high aspect ratio features with great fidelity. Furthermore, structured PMMA substrates provide an excellent master for the production of high-aspect ratio molds for both hot-embossing and injection molding techniques.

Plasma etching

The fundamental action of plasma etching is similar to that of laser ablation, except that gaseous plasmas rather than radiation are used to attack the polymer surface. Oxygen and argon plasmas have been successfully used to fabricate microchannel networks in materials such as polyimide, PMMA, polytertrafluoroethylene (PTFE) and fluoroethylenepropylene.[27,28] Importantly, plasma methods have been shown to be

Fig. 3 Laser-ablated network of curved microchannels (50 µm width) in polycarbonate. Courtesy of Exitech Limited, UK.

successful in fabricating narrow reservoir and flow-through holes.

Bonding

Although conceptually trivial, one of the key challenges in creating any fluidic device is releasing an effective seal between the structured polymer layer and a coverplate. As stated, bonding methods for glass are often convoluted and involve the application of high temperatures for extended periods of time. For polymer-based systems a number of alternative options exist.

At the most basic level gluing substrates together often affords an adequate seal. However, this approach is often limited by the high risks of channel blockages. Thermal lamination with a PET/PE film (20-40 μm) is a more common solution to the bonding problem.[22] Fig. 4 shows a cross section through a PC chip laminated with a PET/PE film. Lamination can be achieved at temperatures around 100 °C using standard industrial lamination apparatus. Due to the susceptibility of channels to blocking, normal adhesive layers are often omitted in the bonding process. For elastomeric polymers sealing is a trivial operation. As noted, conformal contact between the structured layer and cover provides for a non-permanent seal, whilst plasma oxidation affords a permanent (and leak-free) bond with a variety of materials (including glass, PE, PS, silicon and quartz). In addition, it has been recently shown that brief exposure of polymers such as PET to oxygen plasmas activates the surface to allow for both a perfect seal at low temperatures and uniform channel surface properties.[23]

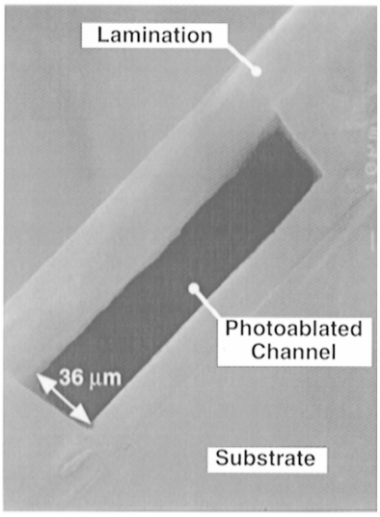

Fig. 4 Laser-ablated microchannel laminated with PET/PE film. Reproduced from ref. 11 with permission.

Other methods including pressure-induced sealing[29] and laser welding[30] have also been reported.

Polymer chips in action

The message is clear: polymers can be machined using a diversity of techniques to create high-quality microfluidic devices at low cost and in large numbers. Nonetheless, how good are these devices at processing chemical and biological systems? And do they compare favorably with more established glass devices?

As discussed, one of the most common methods to maneuver fluids through fluidic networks is *via* electrokinetic pumping. Effective electrokinetic pumping is dependent on a number of issues. First, the substrate material should possess good electrical insulating properties so that the potential drop is across the fluid sample and not through the substrate material (the primary drawback of silicon in electrophoretic applications). Second, when a field is applied across a fluid-filled channel significant Joule heating may occur. Although, the small dimensions typical of most microchannels aid heat dissipation, the substrate material should possess a high thermal conductivity. Third, surface charges on the walls of microchannels or capillaries generate a bulk solvent flow (electroosmotic flow or EOF) towards the cathode. The high density of surface charges in materials such as fused silica generate a large EOF so that during electrophoresis all species (regardless of their charge) move towards the cathode (and can be detected at a single point downstream of the injector). Most polymers exhibit greatly reduced EOFs (due to a lack of ionizable groups),[10] and thus it is important that surface charge characteristics be controllable.

A wide variety of polymer CE-chips have been reported. The first report of polymer based CE microdevice was made in 1990 by researchers at Pharmacia Biosensors.[31] The device, cast from silicone rubber, was sealed between glass plates and used to separate a ϕX174 phage restriction digest in less than 15 min. Due to its facile processing PDMS has proved a most useful substrate material for such applications. Carlo Effenhauser and colleagues at Ciba Geigy reported the first miniaturized CE system in PDMS in 1997.[17] They demonstrated efficient separations of both DNA restriction fragments and peptides within gel filled channels and reported detection of DNA fragments at the single molecule level. Subsequently, George Whitesides′ group at Harvard University pioneered the development of PDMS microsystems for a variety of applications *via* rapid prototyping[19] and replica molding techniques.[19,16] Their electrophoretic studies have focussed on the separation and analysis of species such as amino acids, DNA restriction fragments and peptide charge ladders.[19] A common problem with PDMS is poorly defined EOF[32] and it is suggested that the nature of EOF is highly dependent on the method used to seal the fluidic device. Charles Henry and co-workers at Mississippi State University recently reported a successive multiple-ionic-layer approach for coating PDMS microchannels.[33] By applying a bilayer consisting of a cationic polymer (polybrene) and anionic dextran sulfate, EOF can be generated and controlled in a precise manner. Many other polymeric materials have been used to fabricate CE-chips. For example, Hubert Girault and associates at Ecole Polytechnique Fèdérale de Lausanne have exploited laser photoablation methods for the production of CE chips materials such as PS, PC, cellulose acetate and PET.[22,23] The actual process of ablation generates increased EOF and treatment of substrates with an oxidative plasma affords direct lamination of PET/PE films without the use of adhesives. Recently, researchers at the National Institute of Standards and Technology (NIST) have also reported the use of laser ablation to structure PET, PC, polyvinylchloride (PVC) and PMMA substrates.[24] Interestingly, the authors note that changing the ablation atmosphere leads to marked changes in surface chemistries and also in observed electroosmotic mobilities.

Many other polymers have been used to structure chip-based CE devices. These include the use of acrylic and polyimide chips for DNA sequencing applications[9,11] and parylene[34] and Zeonor[35] for CE-mass spectrometric analysis of small organic molecules. More extensive details of polymer-based CE devices can be found in excellent reviews by Becker and Locascio[8] and Ricco *et al*.[9]

A key feature of many polymeric materials is superior biocompatibility when compared to silicon and glassy materials. This has important implications for the use of polymer systems in applications such as DNA analysis, cell handling, clinical diagnostics and PCR. Indeed, many microfluidic companies have focussed commercialization on polymer devices, combining superior physical properties with the ability to produce high-volumes at relatively low

costs. For example, Washington based Micronics Inc. provide microfluidic technologies for a variety of life science applications.[36] Devices consist of multiple layers of laminate materials (*e.g.* Mylar) that are structured *via* stamping or laser cutting. The fabrication process is both fast and versatile and has yielded a number of distinct microfluidic elements for microcytometry (Fig. 5), separation and detection.[37] Another promoter of polymer based chips is Acalara Inc. based in Mountain View, California.[38] The company is applying advances in microfluidics to genetic analysis, drug screening and optimization and clinical diagnostics. Using molding and embossing methods plastic chip devices have been used successfully in rapid, parallel genotyping[39] and electrophoretic-based enzyme assays for high-throughput screening.[40,41]

As stated, due to the easy machining and good biocompatibility characteristics of PDMS several microfluidic systems for biological applications have been reported. These include microfabricated cell sorters by Stephen Quake[42] and Robert Austin,[43] microfluidic devices for the patterning of cells and proteins on planar surfaces,[44,45] and microfluidic systems for the sizing and sorting of DNA.[46] In addition, although elastomeric materials are ideal for 'low-tech' prototyping applications their versatility in commercial applications is just as exciting. For example, San Francisco based Fluidigm has taken the novel approach of fabricating microscale pumps and valves directly within flexible elastomeric chips. Using multi-layer soft lithography, microfluidic structures can be fabricated in just a few hours, with targeted applications including cell based assays, genomic analysis, protein analysis, gene expression, and integrated biological sample preparation.[47] More details about microfabrication in soft materials can be found in informative reviews by Quake and Whitesides.[16,48]

One of the most important reactions used in molecular biology is the polymerase chain reaction. Several microfabricated structures for performing PCR have been reported in glass and silicon,[49] and more recently there have been reports of polymer based devices. For example, Rolfe Anderson and colleagues at Affymetrix have described a microstructured polycarbonate device for multi-step genetic assays. The highly-integrated system was able to perform DNA extraction, sample pre-concentration, DNA amplification and nucleic acid hybridization in an integrated form.[50] In addition, researchers at Motorola Inc. have more recently reported a polycarbonate PCR/CE microdevice fabricated using compression molding.[51] Many other polymer-based microfluidic systems have been reported. These include PET devices for immunosorption measurements,[52] PDMS microfluidic DNA sensors,[53] microsystems for cell growth[54] and diffraction gratings based on microfluidics.[55]

The verdict

It is evident from this cursory analysis that a vast array of polymer-based materials and associated structuring tools have been developed to address the needs of modern day microfluidics. Due to a wide range in material properties polymers and plastics will undoubtedly play as important a role as more established substrate materials such a glass and silicon in both research and commercial environments. Much of the commercial research into polymer-based devices has stemmed from the need for mass-produce devices at low-cost. Although fabrication infrastructure will always be costly, the establishment and maintenance of large-volume embossing or injection molding facilities is far more cost-effective when compared to more conventional lithographic methods.

To date the primary applications of microfluidic technology lie within the bioanalytical sciences arena, with particular emphasis on genetic analysis, screening and assay technology. Polymers are ideally suited for many of these applications due to their excellent solvent- and biocompatibility and variable surface properties. In addition, many polymers have been developed over a number of decades as blood- or tissue-compatible materials for *in vivo* applications.[56] Efficient structuring of these materials may even allow for microfluidic devices to be implanted under the skin and programmed to release tiny quantities of drugs at precise times or monitor key physiological parameters.[57]

A primary issue that will in part define the eventual success of polymer substrates is the development of well-defined surface chemistries that can be used to enhance or eliminate reagent adsorption onto microchannel surfaces, vary electroosmotic flow and allow incorporation of other functional elements such as detectors. However, a drawback of many polymers is poor chemical resistance to non-aqueous solvents.[8] The application of microfluidic technology to chemical production and drug discovery (where a more diverse range of solvents are encountered) is a growing area of interest. Consequently, it is clear that the development of new materials or modification of existing polymers with superior solvent compatibility will be a key challenge over the next five years.

In conclusion, it is fair to say that polymer microfluidic technology is now an established yet growing field within the Lab-on-a-Chip market. The diversity of both materials and machining methods can only bode well for future applications, and yes, perhaps plastic is fantastic…

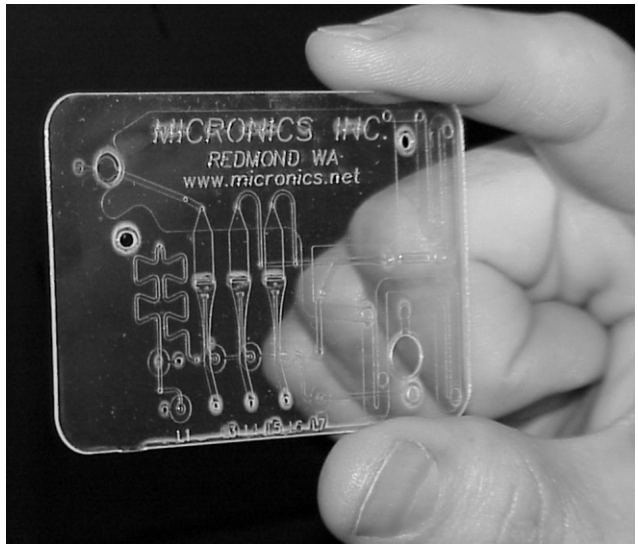

Fig. 5 Disposable microcytometer chip fabricated from optical grade Mylar. Courtesy of Dr B. Weigl, Micronics Inc., US.

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