Biocompatible bonding of microfluidic consumables

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One of the crucial steps in the production process of polymer microfluidic products is bonding. Whether it concerns hermetically sealing a microfluidic system or the assembly of on-chip components, the quality of the bond determines whether the chip functions properly or not. Successfully carrying out a bonding procedure requires a great deal of knowledge of material properties and of the different bonding techniques available.

Biocompatibility in microfluidics production

Extensive use of microfluidics in life sciences and medical research has demonstrated the need for devices that are of excellent quality without making use of materials that can affect or even damage the biological test material. Furthermore, microfluidic devices are being used increasingly close to the human body, for example in the form of microneedles or even implants. For this reason also, it is of the utmost importance to work exclusively with harmless substances. To meet these requirements, the entire production process of a chip must be closely examined in order to remove or replace all process steps and/or additives that could be harmful to the functionality of the device or to its user.

Bonding is a fundamental part of the production process of microfluidic devices and it often involves the use of added substances. Generally speaking, there are three

Mask alignment and bonding tool

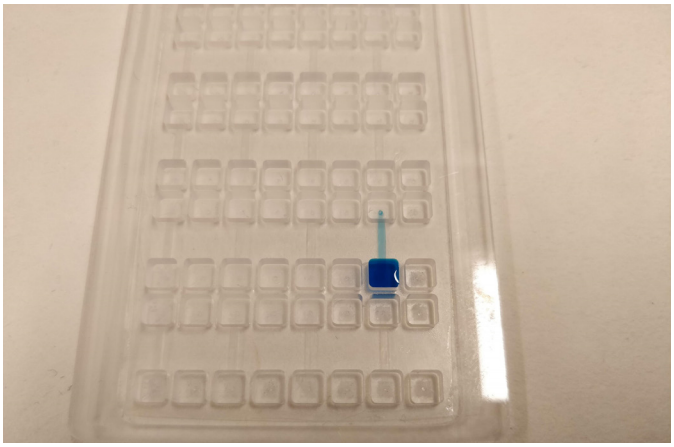
methods of bonding: adhesive, chemical and thermal bonding. Below, we will discuss how these three methods can be used for biofriendly or biocompatible bonding. The term biocompatible bonding as explained in this article is defined as the compatibility of a material or a process with living tissue. It is a broad term however, and it is good to keep in mind that a substance or material that is not compatible with a certain application may well be with another.

Adhesive bonding

Adhesive bonding is an indirect bonding method: it makes use of an added substance in the form of an adhesive layer. Two substrates are connected by means of, for example, a glue or tape.

Adhesive bonding with tape

Bonding with the use of tape is also called adhesive carrier adhesive bonding. To ensure that sensitive content is not damaged, there are different types of tape available that can also be tailored per application by changing the adhesive composition and/or the adhesive carrier thickness and material. Some tapes are more biocompatible than others, which means that often a compromise has to be found between biocompatibility and other critical to quality requirements such as transparency and bond quality. In tape bonding, the whole top surface (lid) is covered in tape, which means contact with the (bio)liquids in the fluidic system is inevitable.



Prototype device - polymer bonded with foil

The thickness of the adhesive layer can be tailored depending on the application and required bond strength. Typical adhesive thicknesses which are used in microfluidics start from a few tens and go up to a hundred micrometers. The adhesive carrier can also be adapted based on the application and its thickness ranges between a few tens to a few hundreds of micrometers.

Adhesive bonding with glue

This is much like bonding with tape. The glue layer is a thin and intermediate layer, which is a few micrometers thick. There is a large variety of glues available, which can be altered to achieve the wanted composition. The glue can be dispensed, transferred, coated or printed onto the surface. The glue is only applied directly at the location of the bond and not onto the entire surface of one of the bond layers. Therefore, contact between the liquids and the glue is limited. UV bonding is a specific type of glue bonding in which a UV curable adhesive is applied on the surface, after which the bond is finalized by exposure to UV light. The advantage of UV curable adhesives is that the adhesive cures when the UV light is applied. Subsequently, UV curable adhesives cure in a much more controllable way than for example heat/time curable adhesives.

Biocompatibility of adhesive bonding

Bonding using adhesives, although still applicable to many cases, does not score very well on the biocompatibility scale. We saw that it is often inevitable that the test fluids come into contact with the adhesives. The upside is that there is a growing variety of tapes and glues available, including biofriendly variants. A pressure step is always part of adhesive bonding, and a heating step can be used to strengthen the bond, but mostly this does not require very high temperatures and in some cases isn't necessary at all. UV curable adhesives are used without the use of heat. Techniques such as degassing prior to bonding or thorough cleaning can be used to mitigate negative effects of adhesives on biological compounds.

Thermal bonded Point-of-Care device. Courtesy of © Fraunhofer IIS / Paul Pulkert

Thermal fusion bonding

Thermal fusion bonding is a direct bonding method. No additional materials are used to achieve the bond: the polymer substrate material itself allows the bond to be formed. This is achieved by applying heat and pressure. The heat is increased until the polymer is close to its glass transition temperature and begins to soften. Then the parts to be bonded are firmly pressed together and after cooling a strong bond is formed. Application of the heat and the pressure needs to be done in a very accurate manner, because if either of them exceeds the required value, it could significantly deform the (channel) structures in the substrate.

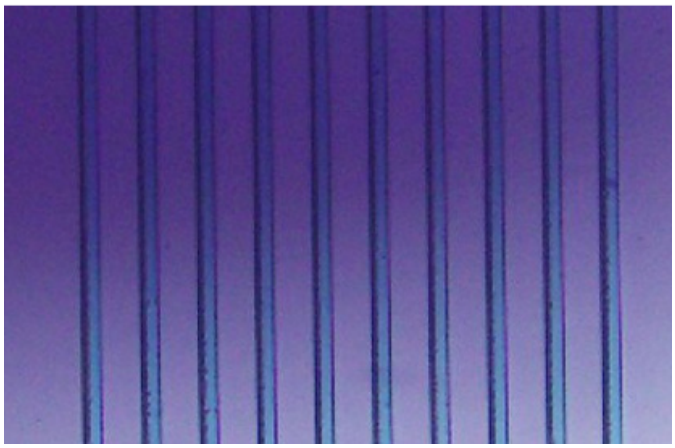
Biocompatibility of thermal fusion bonding

This process requires no external additions, which makes it a very clean bonding process. A factor to take into account however, is that elevated temperatures are involved. This is not a problem when the fluidic platform is first used after the bond has formed, but can be a point of concern when working with 'preloaded' substrates. Here, a substrate is functionalized with biomaterials (usually in a dried form) that will act as a reagent during the assay. Surface functionalization takes place before bonding, which means the on-chip biomaterials might not survive the elevated temperatures of thermal fusion bonding.

This type of bonding is especially useful for example for organ-on-a-chip applications, because no glues or solvents are used and the culturing will take place after the bonding process.

Solvent assisted bonding

In solvent assisted bonding, the substrate material is treated with a solvent or a solvent dilution. Solvents can be used in a liquid or in a vapor phase. Application of the solvent causes the upper surface (few nanometers) of the polymer to dissolve. By bringing the surface to a semi-liquid state, it becomes suitable for bonding. Next, the substrates are pressed together and the temperature is marginally increased to allow a strong bond to form. High temperatures are not necessary. For example 40 °C is sufficient, which is lower than typically used in thermal fusion bonding. Because of the slightly elevated temperatures, the solvent evaporates and no residues are left in the microchannels. There will remain solvent residues inside the bond itself, because this is a sealed space that leaves no possibility for the evaporated solvent to escape. There is a concern that the solvent might leach in the channels at a later stage. For now, however, this technology has been tested successfully for a duration of six months without issues.



Extremely small (< 10um) embossed channels, closed by solvent assisted bonding

Biocompatibility of solvent assisted bonding

As the solvent evaporates during the heating process, the product that is left is solely formed out of the bulk material. It carries no additional substances, except for the residues of solvent that might be left inside the bond. This would not be harmful for regular microfluidic testing, however in certain applications (e.g. where the microfluidic component has to enter the human body) the concern of non-biocompatibility is valid and strong.

Plasma assisted bonding

The principle of solvent assisted bonding produces a very pure end result, since the polymer itself forms the bond. This generates a product of homogeneous quality. Adding the solvent to get the material into a 'bondable' state is a disadvantage however. An alternative is offered by plasma assisted bonding. Plasma assisted bonding is a combination of thermal fusion bonding and low pressure plasma. The substrate material is activated by means of low pressure plasma generation. The substrate is placed in a vacuum chamber, in which the plasma is created by bombarding the surface with oxygen ions. The reduced pressure environment allows the plasma to be formed and sustained even at room temperatures. The plasma, in fact a non-solid state of the material, increases the material's adhesion potential. After plasma generation, the bond is formed the same way as in thermal bonding: by applying heat and pressure. This is why this technique is also called 'plasma assisted thermal fusion bonding'. The plasma step generates a very clean surface and therefore the bond is very strong. Low-pressure plasma activation is also used in cleaning processes. Plasma cleaning results in surfaces free of organic contamination. The process takes only a few minutes per batch and gives better results that traditional wet chemical cleaning, which, despite thorough rinsing and drying, often leaves behind organic residues.

Plasma assisted bonding at Micronit

Biocompatibility of plasma assisted bonding

The greatest advantage of plasma assisted bonding is that it reaches the bondable state of the polymer without the use of chemicals. Temperatures used in the bond fortification step can be slightly lower than in thermal fusion bonding. This can still pose a danger to biomaterial that is preloaded onto the polymer substrate.

Welding

Welding is a somewhat more industrial bonding method that scores very well on biocompatibility. Currently, ultrasonic welding and laser welding are the two most popular welding techniques for microfluidic devices.

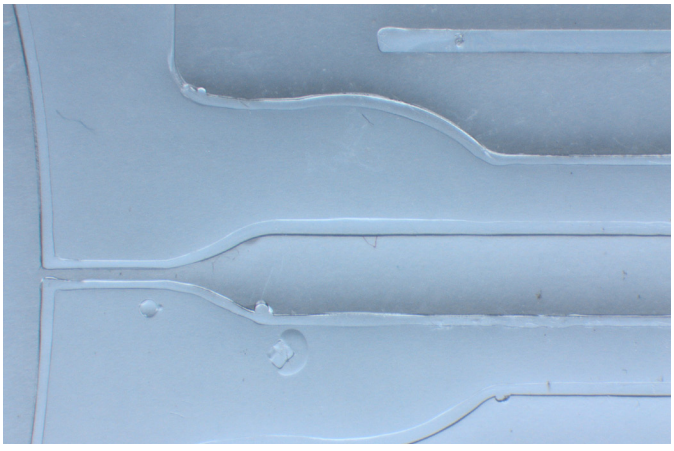
Ultrasonic welding

Ultrasonic welding is a technique that uses high-frequency vibrations that 'shake' the polymer parts together into a bond. The parts to be bonded are lightly pressed against each other to ensure good contact of their surfaces.

Ultrasonic welding involves energy directors which are directly molded on one of the two substrates and basically form a flat top pyramid shaped 'ridge' that sets out the path of the future bond. The thinner top of this ridge is the first part that touches its counterpart. It carries the highest stress, and is therefore the first section to melt under application of ultrasonic energy. The energy directors run along both sides of the microfluidic channel and in this way a hermetically sealed system is created.

Ultrasonic welding can also be used to integrate functional elements like membranes or on-chip components such as blisters with reagents or fluidic connections. The size of the energy directors is at its lowest about 50-100 microns in width and height, which makes this technology less suitable for structures that have spacing under 200 microns and are less wide than 100 microns.

Ultrasonic welding offers an extremely fast bonding cycle: the welding process only takes seconds.



Ultrasonic welded COC foils (140+250 µm) - Detail 300 µm channel. Courtesy of INMOLD A/S, NextGen Microfluidics [1]

Laser welding

Laser welding uses a very concentrated laser source that places welds alongside the microfluidic channels. Laser welding takes somewhat more time than ultrasonic welding because the laser beam has to follow the entire path of the required bond. Consequently, if a meandering structure is required, this takes a longer welding time. This opposed to ultrasonic welding, where the preprocessed energy directors have already mapped out the welding route and allow the process to take place in just a few seconds.

Laser welding does offer more flexibility, because the welding path can be determined or altered at any minute, while in ultrasonic welding the position of the bond is already determined during preprocessing, when the energy directors are incorporated in the chip structure during the molding process. In laser welding, the size of the laser beam must be taken into account. It usually takes up between 40 and 100 microns, which is comparable to the size of the energy directors in ultrasonic welding.

Laser welded 200 µm COC foil and 1 mm COC plate. NextGen Microfluidics [1]

Biocompatibility of welding

The advantage of welding is that it causes a solid direct bond without any additions or affecting the base material. Heat is applied very locally and precisely, thus it does not affect the surface that falls outside the bonding scope.

[1] This project has received funding from the European Union's HORIZON 2020 research & innovation programme under grant agreement no. 862092

Risks and advantages

Biocompatible bonding is an important capability in the microfluidics industry and is becoming more and more challenging due to the increasing complexity of the devices. Apart from the biocontent (preloaded or added during the assay), one might also have to deal with multiple layers and on-chip functional elements. All these elements and their physical characteristics have to be taken into account when deciding for a bonding type.

The following scheme sums up the key risks and advantages of different bonding processes.

		Adhesive bonding	Thermal bonding	Solvent bonding	Plasma bonding	Ultrasonic welding	Laser welding
Risks	Risk of damage by heat	Very low risk	Very high risk	Low risk	High risk	Very low risk	Very low risk
	Risk of damage by added substances	High risk	Very low risk	Medium risk	Low risk	Very low risk	Very low risk
	Risk of blocking or deforming channels	Low risk	High risk	Medium risk	Medium risk	High risk	Low risk
Advantages	ISO 13485/GMP compatibility	Good	Good	Negative	Okay	Good	Very good
	Optical quality	Okay	Very good	Very good	Very good	Very good	Negative*
	Bonding strenght	Okay	Okay	Very good	Good	Very good	Very good
	Process speed	Good	Bad	Okay	Negative	Very good	Okay

* For laser welding, most of the times a non-transparent / absorbing layer has to be used, preventing transparency on one of the two sides of the device.

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Christos has a background in manufacturing engineering and fluid mechanics. He started his career at Micronit in 2016 and fulfilled several roles in process and product development. Currently, Christos is managing the technical roadmap within Micronit and in this role he is responsible for the introduction of new technologies and the development of current technologies to higher technology readiness levels. Certified Green Belt in Design for Six Sigma, Christos is also involved in customer projects connecting application requirements to technological solutions.

About Micronit

Micronit offers a broad range of bonding capabilities so that the requirements for specific applications and materials can be met.

Micronit bv, founded in 1999, with development and manufacturing facilities in the Netherlands and Germany, provides innovative lab-on-a-chip and MEMS solutions using micro- and nanotechnologies. Solutions that help customers improve their products and research, contributing to the quality of life.

Micronit is ISO 9001 and ISO 13485 certified.

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