Research Progress of 3D Printing Microfluidic Chip

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Abstract. Because of the advantages of microfluidic technology, such as high detection speed, high accuracy and low reagent loss, it has obvious advantages over the traditional detection technology. So recently, microfluidic technology has been widely used in life science and medical diagnosis. However, the microfluidic chip processing technology is mostly developed from semiconductor processing technology, which has the characteristics of high cost and high technical requirements, which are also important factors limiting the development of microfluidic technology. In recent years, 3D printing technology has become more and more mature, so using 3D printing technology to make microfluidic chips has attracted the attention of many researchers. Compared with the traditional microfluidic chip processing technology, 3D printing microfluidic chip technology has been widely concerned because of its advantages of fast design and processing speed, wide material adaptability and low cost. At present, the processing methods of microfluidic chip mainly include micro stereolithography, deposition molding, ink-jet printing and so on. In this paper, the main research progress of 3D printing microfluidic chips at home and abroad and the future development direction are reviewed. At last, the applications of microfluidic chip processing technology in analytical chemistry, life science, medical diagnosis and other fields are prospected.

1. Introduction

The term microfluidics appeared in the early 1990s, referring to the technology of operating and controlling fluid on a micro-scale [1]. After more than 20 years of development, microfluidic technology has developed from a single functional fluid controller to a multi-functional integrated and widely used microfluidic chip technology, which has been widely used in analytical chemistry [2, 3], medical diagnosis [4, 5], cell screening [6, 7], gene analysis [8, 9], drug transport [10, 11] and other fields. Compared with traditional methods, microfluidic technology has attracted the attention of many researchers because of its small sample size, high detection efficiency, low cost and easy integration with other technical equipment, good compatibility, and the potential to achieve portable detection devices. Microfluidics, also known as lab on a chip (LOC), refers to the construction of a chemical or biological laboratory on a chip of several square centimeters. At present, most of the microfluidic chip manufacturing technology is inherited from the semiconductor industry, which has a variety of processing procedures and relies on advanced equipment with high price. The common processing methods in the fabrication of microfluidic chips include: surface micromachining [12], soft printing [13], embossing [14], injection molding [15], laser ablation [16], etc. These processes need to be completed...
in the super clean room. The process is complex, needs to occupy a lot of space, and requires experienced design and processing personnel [17].

In recent years, with the rise of 3D printing technology, more and more researchers try to use 3D printing technology to directly print microfluidic chip, or print out the mold of microfluidic chip that can use PDMS inversion. 3D printing also known as additive manufacturing. It is a process which builds three-dimension objects from a computer-aided design (CAD) model. 3D printing is mainly a process of continuous addition, in which raw materials add layer by layer under the control of computer. At the very beginning, 3D printing was used in the field related with art and fashion, people were surprised by the clothes made by 3D printing process. As the technology matures, it can be used in medical items and prosthetics. As the technology of 3D printing improves and costs fall, microfluidic device is finally ready for widespread use.

By using 3D printing technology, the processing of microfluidic chip can be significantly simplified, and the selection of printing materials is also very flexible. In addition to various polymer materials, biological materials can also be directly printed [18, 19]. Generally, the 3D printing process of microfluidic chip only needs to print the microfluidic chip directly after the design is completed. Compared with other microfabrication technologies, it greatly reduces the technical threshold and processes cost of microfluidic chip, which has a very positive significance for the promotion and application of microfluidic chip technology. In recent years, the application of 3D printing microfluidic chip technology in biomedical detection field has developed rapidly. There are many 3D printing microfluidic chips used in cell analysis and detection [20-22], drug transport [23] and other fields.

In this paper, several kinds of 3D printing microfluidic chip technologies are discussed, including micro stereolithography, fused deposition and 3D ink-jet printing, which have developed rapidly and are more common in recent years. The applications of these technologies in analytical chemistry, biomedical detection and other fields are reviewed, and the future development of 3D printing microfluidic chip technology is prospected.

2. Introduction of 3D printing microfluidic chip technology

2.1. Application of micro stereolithography technology in microfluidic chip processing

Most of the processing technologies of microfluidic chips are derived from semiconductor manufacturing technology. However, micro stereolithography (μSL), which can be used in microfluidic chip processing, is originated from stereolithography (SLA) in the field of industrial design. Micro stereolithography is a three-dimensional structure formed by controlling the exposure light source, curing the photosensitive resin layer by layer and stacking layer by layer. Although the micro stereolithography technology does not really "print" the required structure, but its processing process is very similar to 3D printing through the selective layer by layer curing of the liquid photosensitive resin. This paper also ascribes the micro stereolithography technology to one of the technologies that can be used for 3D printing microfluidic chips.

Stereolithography has a history of more than 30 years [24]. Due to the limitation of precision, the early stereolithography is not suitable for micromachining. In recent years, with the progress of technology, stereolithography technology has been gradually applied to the field of micromachining, and the common desktop micro stereolithography equipment has been able to achieve a precision of 200 μm [25, 26]. A new micro stereolithography technology based on two-photon polymerization (2PP) [27, 28], can improve the precision by 10 μm.

Because of the convenience and high precision of the manufacturing method, more and more researchers began to apply the micro stereolithography technology to the microfluidic chip processing. At the same time, the light source that can be used for micro stereolithography is not limited to UV light source (UV) [29, 30]. Many researchers began to use LED [31, 32] laser [33-35] as light source for curing photosensitive resin. With the diversification of exposure light sources, the photosensitive resin used in micro stereolithography is no longer limited to UV sensitive epoxy resin and acrylate polymer
materials. In recent years, researchers began to use new polymer materials such as polyhydroxy fumarate (PP), diethyl fumarate (DEF) [36], accura60 [37].

![Figure 1](image)

**Figure 1.** Comparison between (a) PDMS/plastic molding and (b) stereolithography for the fabrication of polymer-based microfluidics chips

Figure 1 shows the process of microfluidic chip machining by traditional micromachining method and micro stereolithography method, respectively. The common processing process of microfluidic chips based on polymer materials is shown in Fig. 1(a). The first step is to make a mold, and use photolithography and other means to process the photoresist on the glass or silicon wafer. The commonly used photoresist is SU-8 [38]. The second step is to make use of the first step of die inversion, the common materials used for microfluidic chips are PDMS and so on. For microfluidic chips with multi-layer structure, the above two steps need to be repeated for each layer structure. The third step is to bond another layer of material to seal the flow channel. For microfluidic chips based on PDMS materials, the surface of PDMS needs to be modified by plasma [39] or UV [40] before bonding, and then a layer of glass substrate is bonded to close the microchannel. Finally, the opening of the microchannel entrance and exit are needed to process, which is usually completed by using a special punch or laser.

Compared with the traditional microfabrication method mentioned above, the whole microfluidic chip manufacturing process can be completed in one step, as shown in Fig. 1b. In the actual processing, the three-dimensional microfluidic chip structure is converted to the section data with specific thickness by computer. And then the photosensitive resin is exposed and solidified by precision controlled ultraviolet, LED or laser, and the thickness is controlled by the lifting table to realize the processing of the whole 3D microfluidic chip. The microchannel in the microfluidic chip, the opening of the chip inlet
and outlet, and the closure of the microchannel are all realized in the same step, which significantly improves the efficiency and reduces the error caused by human factors in the traditional processing methods.

There are several advantages of using stereolithography technology. The first one is high precision and fine details, due to the width of each layer applied in stereolithography is about 0.05 to 0.10 mm, so it is possible to obtain prototypes with a very realistic finish and complex geometric shapes. The second one is smooth surface. In stereolithography, the resulting parts have a smooth surface, with the option to choose between a number of resins for different renderings.[41] The limitation of stereolithography technology is fragility. The 3D printed object is made of the same resinous material. The resulting part is more fragile than the final part. If the quality of finish allows for functional prototypes, stereolithography does not allow for parts that can be used for mechanical testing.[42]

**Figure 2.** Schematic diagram of laser direct writing system based on two-photon aggregation

Based on two-photon aggregation laser 3D Direct Writing provides an effective solution, and is currently the most effective technology to achieve nanoscale 3D printing. Different from the traditional micro stereolithography (a single photon micro stereolithography process), 3D printing based on two-photon aggregation laser direct writing is based on two-photon aggregation principle (or multiphoton absorption). Two-photon polymerization is a process of photopolymerization initiated by two-photon absorption. Two-photon absorption refers to the absorption of two photons by a molecule of matter at the same time. The two-photon absorption mainly occurs at the super intense laser focus generated by the pulse laser. The laser intensity at other places on the optical path is not enough to produce two-photon absorption. Moreover, due to the long wavelength and low energy of the light used, the corresponding single-photon absorption process cannot occur. Compared with the single-photon lithography process, the two-photon process has good spatial selectivity. The two-photon polymerized laser direct writing 3D printing takes advantage of the characteristics of the two-photon absorption process, which has good material penetration and high spatial selectivity. Its basic principle is shown in Fig. 2 [43].

**Figure 3.** Flowmeter based on photometer 3015 photosensitive resin processed by two-photon polymerization micro stereolithography method. Due to the high precision of two-photon polymerization micro stereolithography, the length and width of the flowmeter are only 30 μm and 15 μM. This flowmeter is placed in the microchannel. By observing the deflection of the flowmeter in the microchannel, the minimum flow can be measured as 1 μL/min. In the actual measurement, the flow data in the microchannel can be obtained by comparing with the standard.
2. Application of 3D printing technology of fused deposition in microfluidic chip processing

Fused deposition modeling (FDM) 3D printing technology, a type of 3D printing where a heated thermoplastic material is extruded from a motor-driven nozzle head, was invented by Scott Crump in 1988[44]. It extrudes the filamentous thermoplastic material from the heated nozzle, and deposits the melt layer by layer according to the predetermined trajectory and rate, so as to realize the three-dimensional forming. Due to the advantages of simple printer structure, convenient operation, fast forming speed, rich material types and low cost, fdm3d printing technology has been more and more applied in various fields. It is a 3D printing technology with wide application field, high maturity, great application value and broad prospect.

In the practical application of various 3D printing technologies, most low-cost 3D printers are based on this technology. In some literatures, the fused deposition molding technology has become the fused deposition technology (FFF) [45, 46]. Compared with other kinds of 3D printing microfluidic chip technology, FDM technology has a wide range of adaptability in material selection. In theory, almost all thermoplastic polymer materials can be used in the melt deposition molding technology. The wide adaptability of materials has brought great advantages to the application of FDM technology in 3D printing microfluidic chips. In use, polymer materials can be selected flexibly according to the actual needs of experiments (physical/chemical properties, biocompatibility, corrosion resistance, etc.), and even the microfluidic chips made of different polymer materials can be realized by replacing fuses.

Using FDM based 3D printing technology, software is needed to dissect the 3D model layer by layer. The thickness of each layer varies from 0.1-1.0mm according to the different printers. Then the software calculates each layer separately to plan the reasonable movement path of the nozzle. The typical FDM processing process is generally as follows: the wire rod of polymer material is sent to the metal nozzle with heating device through gear and other mechanisms. The polymer material is heated above the glass transition temperature, and the softened polymer material fuse is ejected from the nozzle to the bottom plate for cooling and curing. In general, the fuse nozzle of 3D printing equipment based on FDM can move in three directions at the same time, forming a three-dimensional structure by stacking the fuse layers. In order to prevent the printed material from warping during the cooling process [47], some melt deposition molding printing devices are equipped with a heating base plate. Some of the more advanced melt deposition molding printing devices are even equipped with two or more printing heads, which can print different kinds of polymer materials at the same time.

He et al. [48] modified the nozzle part of 3D printer by melting deposition forming so that it can print heated sugar fiber and liquid PDMS through double nozzles, respectively, in which PDMS is used as the auxiliary support material of sugar fiber when printing 3D structure.

The 3D printing technology based on FDM in the field of microfluidic chip processing shows its wide adaptability to processing materials and good application prospects in the field of life science and chemistry. However, there are still some defects that need to be improved. The first is the printing accuracy, which involves two aspects. The first one is the printing accuracy in the horizontal plane (X-Y) direction and the accuracy in the layer height (Z) direction. The printing accuracy in the same horizontal plane is affected by the size of nozzle and the accuracy of stepping motor, generally about
200-500 μm. Wang et al. [49] improved the accuracy to 100 μm by heating polymer materials in advance. In terms of layer height, the 2-axis accuracy of FDM printer commonly used at present is 100-500 μm, but it can not fully meet the height requirements of microchannels in microfluidic chips. In addition, the surface roughness and wall perpendicularity of the microfluidic chip printed by FDM technology have some disadvantages compared with other processing methods, which are urgent problems need to be solved in the future research.

2.3. Application of inkjet 3D printing technology in microfluidic chip processing

Inkjet 3D printing technology was first proposed by bonyar et al. [50], which is a type of 3D printing that each layer inbuilt onto a tray through an inkjet head. It is all through the printer's nozzle array to spray small ink droplets onto the bottom plate. Different from ordinary ink-jet printers, ink-jet 3D printing technology generally prints the small droplets of photosensitive resin on the bottom plate. Meanwhile, the resin is solidified by the UV light source installed on the nozzle. Similar to FDM technology introduced before, inkjet 3D printing technology also processes three-dimensional structure through layer by layer printing. Inkjet 3D printing technology is a kind of inkjet powder binding 3D printing technology. The operator only needs to import the 3D data of the mold into the control computer of the 3D printer, the software of the system will automatically convert the 3D data into the 2D section, and print out the adhesive by using the ink-jet printing head to stick the sand together, stack layer by layer, and directly produce the sand mold/core. Compared with the traditional technology, the first is to omit the mold making process and shorten the production cycle of the product; the second is to directly make any complex shape of the sand mold, which is not limited by the mold processing technology; the third is to ensure the accuracy of the sand mold. Combined with the reasonable design of casting system, the yield of castings can be greatly increased and the production cost can be reduced. According to the cases that have been implemented at present, the trial production cycle of products can be shortened from three months to three weeks by using the ink-jet sand mold 3D printing technology, thus greatly increasing the number of development iterations and significantly improving the yield and quality of mass production.

Figure 4 shows the microfluidic chip mold (yellow) made by inkjet 3D printing technology and the microfluidic chip based on PDMS material made by reverse mold, which is used for biological sample mixing and transportation. The Eden series inkjet 3D printer (Israel objet company), widely recognized in the field of inkjet 3D printing technology, is used. With fullcure 720 photosensitive resin and fullcure 705 support material, the accuracy of 40 μm in XY plane and 16 μm in two directions can be achieved, which can meet the accuracy requirements of microfluidic chip in most cases. It should be pointed out that the accuracy of the actual printing structure not only depends on the motion accuracy of the mechanical system on X, and 2 sides but also depends on the size of the smallest ejectable droplet [51].
3. Application of 3D printing microfluidic system

Microfluidic chip manufacturing technology based on 3D printing has the incomparable flexibility of traditional microprocessing technology. Generally, the whole design and processing process can be completed in a very short time, which has a strong adaptability for the research of life science and medicine. On the other hand, the application of 3D printing technology significantly reduces the cost of microfluidic system, which has a very positive significance for the promotion and application of medical diagnosis technology based on microfluidic system in underdeveloped countries and regions.

![Figure 5](image1.png)

**Figure 5. Using Autodesk fusion 360 to design an object**

There are generally four steps of 3D printing: modeling, slicing, printing and assembly coloring. The first step is modeling, which is to design the structure what you want to manufacture. The commonly used software is 3D Max, Maya, fusion 360, etc. As shown in Figure 5, the basic interface of fusion 360. Fusion 360 can integrate industrial design, mechanical design, collaboration, processing and other elements, and provide a perfect solution from design to processing.

![Figure 6](image2.png)

**Figure 6. Printer produced by ultimaker**
After having a model, it is necessary to start slicing. Slicing, in fact, is equivalent to converting the 3D digital model that has been built into the walking path that can be recognized by the 3D printer and the extrusion amount of consumables. After slicing is completed, the digital file is really transformed into the real touchable object. One of the most critical tools to achieve this is the 3D printer. As shown in Figure 6, it is one of the more mainstream 3D printers produced by ultimaker. For this step, we have to decide some details, for example, Ultimaker 2+, PLA yellow 3mm, PLA black 2.85mm. Those details are about the diameter of the printing material flow out of the 3D printer. Some machine can also determine the color of each part of the object. The final step is to assemble and color, that is, to splice the printed parts. some complex structures consist of multiple parts, so they print the whole structure by different parts, and at last, assemble it together. Generally, before assembly, the zero level will be simply polished. As shown in Fig. 7 (a) printed microchip is provided.

![Figure 7. Printed microfluidic channels](image)

Before using the microfluidic chip for detection, the size of the channel in the processed microfluidic chip will be checked first to see whether it meets the requirements of the experiment. Because the size of the printed channel basically belongs to the magnitude of micrometer, it is impossible to measure its size by using the conventional measurement method. It is necessary to use more professional tools. Fig. 8 (a) is a profilometer, which is a device specially used to measure the size of micro nanochannels. The principle of measuring the microchannel width of this device is very simple. Just inject the dyed fluid into the processed microchip, and after a few minutes of standing, when the fluid completely flows into each channel, the obvious channel contour can be seen. At this time, observe whether the fluid has completely filled the whole channel or not. Generally, a professional microscope image will be used to
observe, as shown in Fig. 8 (b), it is a common microscope device. With this device, the outline diagram of the fluid can be observed, as shown in Fig. 9. The profilometer will also get the measurement results of this structure, as shown in Fig. 10.

![Figure 9. Image without flow of the channel, Fluid fills the entire channel](image1)

![Figure 10. This is the result from dektakXT profilometer](image2)

If the measurement results meet the design requirements, the next experiment can be carried out. The above is a general step of using 3D printing technology to process microfluidic chips. If making a microfluidic device is necessary for an experiment, design software can be used to make a blueprint. Then the computer can be linked with a 3D printer and print the device. So the cost of producing a microfluidic device is reduced. As the device using fluid flows is tested, the viscosity of the fluid still need to be considered due to the diameter of the channel is very thin.

With this technology, more complex structures can be printed to meet the different experimental needs. Spivey et al. used a self-made 3D printer based on DLP technology to process the molds of PEGDA (polyethylene glycol diacrylate) materials, and used PDMS to reverse the molds, and made a microfluidic chip for the study of yeast cell aging. For smaller E.coli and other bacteria, Lee et al. [52] used 3D printing technology to process microfluidic system with spiral flow channel, and used the interaction of liquid inertia and magnetic field to separate E.coli combined with antibody in milk. In order to prevent cross-contamination, microfluidic chips used in medical diagnosis and other fields are all disposable. In order to reduce the economic burden of patients, vigorously reduce the cost of microfluidic chips is necessary. In the field of ultra-low-cost microfluidic chip processing, 3D printing technology also shows its unique advantages.

4. Summary and Prospect

According to the technology provided at present, there are many microfluidic devices capable of 3D printing. In practical application, the choice of 3D printing microfluidic chip technology should be comprehensively considered from the aspects of processing cost, material cost, processing accuracy, biological compatibility of materials, chemical corrosion resistance of materials, etc.
As a relatively early and mature 3D printing microfluidic chip processing technology, microstereolithography has the characteristics of high printing accuracy and multiple photosensitive resins. Its disadvantage is that after printing, it needs to be heated and solidified to remove supporting materials and other follow-up work, and the processing process is relatively complex. The technology of 3D printing microfluidic chip based on two-photon aggregation effect is the most accurate among the several processing technologies introduced in this paper. But, it has high requirements for light source, high equipment cost and slow printing speed, which is suitable for the applications requiring high-precision microfluidic chip. Micro stereolithography based on digital micromirror technology has high precision and low cost, which will be the mainstream technology in the future.

Compared with other 3D printing microfluidic chip technologies, the FDM technology has the lowest cost and the widest material adaptability. Almost all thermoplastic polymer materials can use this technology. There are also many mature commercial 3D printers based on fused deposition molding. However, the application of 3D printing technology of FDM in microfluidic chip processing has always been a problem with several reasons. The first one is the extruded material cannot arbitrarily joined at the intersections of the channel. The second reason is the size of the filaments formed by the extruded material are always have larger diameter compared with typical channels used in microfluidics.

In 2006, Professor Whitesides of Harvard University said in his comments to Nature magazine that microfluidic technology was still in its infancy [53]. Ten years later, although microfluidic technology has developed rapidly, it has been widely used in life science, medical diagnosis, analytical chemistry and other fields, it is still in the primary stage of development. Compared with the development of microfluidic technology, the technology of 3D printing microfluidic chip should be in an earlier period. The early microfluidic chip technology based on 3D printing generally used the method of die reversal. The dies based on ABS, PLA, PC and other thermoplastic materials were printed by 3D printing, and then the die reversal was carried out by PDMS [54]. From 2011 to 2012, microfluidic chips with simple flow channels, which were directly printed, began to appear. After 2012, a microreactor based on 3D printing microfluidic chip appeared. In addition to microfluidic channels, more functional devices were added, and even metal electrodes were introduced [55]. In 2013, a paper-based microfluidic chip made of 3D printing appeared [56], and in 2014, a biodetection and drug delivery chip that can be implanted into human body made of 3D printing was realized [57]. In 2015, the development of 3D printing microfluidic chip technology was more rapid, with the emergence of integrated biosensor [58], high-throughput [59], multi-layer chip [60], real-time biomedical detection and other chips. The paper-based 3D printing microfluidic chip technology also ushered in new development, with the emergence of the paper-based microfluidic chip made of 3D printing with integrated metal electrodes [61].

One of the characteristics of the development of modern science and technology is miniaturization and integration. Microfluidic chip technology appears as an interdisciplinary technology at the beginning, so it can integrate with many kinds of technologies, and play the advantages of different technologies to meet more and more complex application requirements. The development of 3D printing microfluidic chip technology is in the ascendant. It is believed that with the continuous maturity of various 3D printing technologies and the emergence of various new materials, 3D printing microfluidic chip technology will have the characteristics of higher integration, integration of a variety of biological/chemical sensors, higher accuracy and lower cost, and will be more widely used in life science, analytical chemistry, medical detection and other fields. At the same time, the low utilization rate of microfluidic chips and the lack of unified standards hinder the development of microfluidic chip market. To penetrate microfluidic chip technology into agriculture and food industry, we need industrial manufacturing technology to solve the loopholes in unified standards; we need to improve the technical requirements of existing microfluidic, change its complexity and high price, and make it a functional system. The emergence of 3D printing microfluidic chip technology also provides researchers with more ideas. Looking forward to the future, 3D printing technology will become one of the most important technical means in the field of microfluidic chip processing.
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