Journal of Biosensors & Bioelectronics
ISSN: 2155-6210

Mekonen et al., J Biosens Bioelectron 2019, 10:1
DOI: 10.4172/2155-6210.1000265

Review Article Open Access

Microfluidics Devices Manufacturing and Biomedical Applications

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Abstract

Microfluidics technology is growing field emerged late 1950. It became popular passing through different historical events, contributing to the inception and growth of the field. From the beginning of inkjets to current enormous medical and industrial applications. It focus on handling fluids in the micro, Nano, Pico even femto liter level through utilizing the physical properties they exhibit while miniaturized. According to our study class of materials are available for microfluidics device fabrication and there are factors to consider in application specific design and microfabrication. In microfabrication technique, we can implement lithography, laser induced selective etching, powder blasting and molding found for fabrication. The medical and research application of microfluidics devices includes Cardiovascular System, Respiratory system, Nervous System, Digestive+Excretory System, Endocrine System, Integumentary System, cell culturing and preparation of scaffolds, therapeutics, diagnostics and preventive system. Multiples channels of biomaterials, which is biocompatible platforms to regenerate and rehabilitate Physiological and pathological conditions of complex tissues and organs. The aim of this paper is to present a paper reviewing on material selection, microfluidics fabrication, medical application and suggesting future prospects of the fields and possible microfluidics device implementation in biomedical field.

Keywords: Microfluidics; Microfabrication; Biocompatible; Biosensor

Introduction

Microfluidics

Microfluidics technology incepted in the 1950, as a technique used in manipulating and controlling of fluids flow in the micro-channels down to femto-liter level aiming to achieve specific goal in the course through microminiaturized tunnels and chambers [1]. This area of science deals with very small volumes of fluids at quadrillionth level of a liter [2]. During the time of microfluidics first emerged purposed to printers of inkjet [3]. The working principle of the printer relies on the microfluidics containing inkjets. Late in the 1970s, a chromatography of gas realized using silicon wafer [3].

The 1980 is a progressive year for microfluidics technology, post 1980s, the pioneer micro pumps and valves come to live [3]. After a progress made in the micro-valve and pumps in the succeeding year many silicon-based microfluidics product being presented to the market and grown to important field to the industries as well for the medical fields. The undeniable fact is after the development of the above-mentioned microfluidic devices it take longer for researchers to come up with part of microfluidic device like micro fluid transport, metering, mixing, separation and valving components. Now days there are different microfluidics for different application [4].

The development of microfluidics technology is emerged from four different contributors of events in the timeline. Microelectronics is assumed to be the genuine hope of microfluidics due the powerfully microelectromechanical system fabrication technique like photolithography, is implemented in silicon microelectronics give chance that we can apply this method to microfluidics fabrication [1]. Molecular analysis is one of the parents for microfluidics, lie on the development of gas-phase chromatography, liquid chromatography of with high pressure and capillary electrophoresis along with these tools there is laser technology introduced and become parent of microfluidics [1].

A unique motivation, which allow microfluidics to rise, is the incidence of biological and chemical weapons for terrorism and military purpose. Department of defense US, funded programs in preparing microfluidics detector of biological and chemicals with potential to be implemented for weapon. The third potential contributor of the field is molecular biology, rising of the genomics in the 1980s, succeeded by additional more micro analytical techniques. These micro-analytics are DNA sequencing need for high throughput with elevated sensitivity and resolution achieved through a novel way of manufacturing and development of the knowledge in the area. There a significant alteration of fluids property while going down to the micrometric level these change in features are used as gate for research and experiments [2]. Microfluidics use of these fluids physical and chemical characters at the microscale.

Microfluidics give significant advantage compared to macro level system of fluids, mass production is feasible and are capable of allowing investigation in micro-volume reagents and chemical along with reducing global cost of application. They made it possible activities to be performed simultaneously due to their compactness which also lessen time required to perform tasks. Microfluidics device can result in excellent data quality and significant control over parameters and process consequently favor for possibility of automation. Chip of microfluidics described to allow automation and open for performing multiple steps reactions, which needs enormous functionalities and small expertise level. Their expertise level extend from detection of toxins to analysis of the nucleic acid like DNA, inkjet production.

Literatures on microfluidics applications in medicine and fabrication

Starting from the most recent one, in 2018 Wen et al. [5] presented

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Received January 08, 2019; **Accepted** February 22, 2019; **Published** March 02, 2019

Citation: Mekonen AA, Abebe SA, Adali T (2019) Microfluidics Devices Manufacturing and Biomedical Applications. J Biosens Bioelectron 10: 265. doi: 10.4172/2155-6210.1000265

a review on microfluidics fabrication of micro particles for biomedical application aiming at materials, techniques of fabrications and structures of micro particles along droplet microfluidics. The study present the contribution made by micro particles with manipulate able features and collective purpose assisted in solving important shortcomings in the biomedical fields. Specifically, in delivering drug, tissue engineering, 3D cell development and mimicking, and sensing of biomolecules. The team recommended post their study that the field is not adequately explored and require additional studies. Prina et al. [6], the research team studied microfluidics device replacement for ocular surface reviewed latest products in the field and find out for successful replacement the manufacturing and design to mimicking the natural structure. Based on their review additive techniques of manufacturing found out to be promising for not only corneal replacement but also for other tissue engineering application of microfluidics. In the year, 2014 Sackmann et al. [7] reviewed literatures for microfluidics present and future trends of microfluidics in biomedical research. The study focuses on progress attained on lab on chip studies and present the clinical and research prospective made. It discussed by the review team adoption of microfluidics in the biomedical research area encountered a problem. As a solution, they suggested researchers to develop thoughtful and planned approaches to insist forward the acceptance of the technology in the field. Jayamohan et al. [8], studied application of microfluidics for molecular diagnostic study the team briefly assessed the microfluidics molecular diagnostic and their application. Now day's microfluidics molecular diagnostic focuses on single disease and this approach is convincing the future microfluidics has to be multiplexed with a potential of screening many different diseases at once. Taylor and Jeon [9], discussed microfluidics for neurobiology application for small and whole organisms and neurons culturing. The team has appreciated the contribution in controlling of cells and unprecedented possibility in the experiment and new approaches of study.

In 2005, Adam et al. [10] reviewed microfluidics for immune sensor application and characterize material used to fabricate them. Most of them produced from glass, polymer and silicone. Among the materials polymer gating priority for researchers and industries as well. The implemented identification finds out to be fluorescence succeeded by electrochemistry. According to the team observation, microfluidics detection resembles the usual immunoassay approach where competitive molecule used to identification of small molecules.

In 2002, Teruo [11] presented a review on PDMS based microfluidics device for biomedical application. Aims to address fundamentals of PDMS based microfluidics devices and their respective purpose assessed for biomedical application in the study. Up on completion of the review the contribution of PDMS based microfluidics in feasibility of microchips for biomedical application discussed. While concluding he has presented integrating approach of devices according to functionality like electrode, heater, sensor, and etc. implemented on substrate can be brought to PDMS based micro-structure for integrating purpose and appreciated the PDMS based devices. Integrating and multiplexing can lead to microchip multipurpose device according to the study.

Materials and Microfabrication Techniques of Microfluidics

Materials for microfluidics

The advancement in MEMS technologies has reached in micro and Nano-fluidics for different applications. It is very important to be careful in selecting a substrate material, which will have significant effect on the efficiency of the microfluidics system [12]. This happen because of the higher surface to volume ratio situated with in these microstructures. There are also additional factors complicating choice of substrate material like electrophoresis and electro-osmotic flows [12]. Generally, in selecting the appropriate material for microfluidics we have to take into consideration materials: mechanical property, chemical inertness, electrical insulation and dielectric, optical transmission, thermal stability and surface characteristics of the substrate. Beyond the mentioned properties, additional parameters such as pressure, temperature and solvent must be considered. Most frequently used material in manufacturing microfluidics devices and their property is summarized in Table 1 below.

Silicone, glass, quartz, metals, elastomers, hydrogels, paper, composite materials, and other thermoset are the very known material applied in microfluidics application [13]. As it has been inferred from the trends semiconductor silicone is the most utilized material for different microelectromechanical system application nevertheless silicone has limitation for this application while tested for voltage-driven pump based on electrophoresis and combining electro-osmotic flow [14]. For application involving chemical reactions with solvent of non-aqueous glass, materials show superior performance, because of glass optical transparency and thermal resistivity. This property of glass made it possible for lab-on-chip to perform detection easily. Not only has this had the accordance inherent surface charged of glass make it best at in supporting electro-osmotic flow property [12].

The well-known elastomer used is PDMS [15]. This is due to its simplicity and cheap manufacturing cost [16]. Its thermal property is suitable for casting even at nanometers of required application [17]. Posting cure peeling is possible for PDMS based microfluidics is because of its surface tension property [16] chips made from PDMS of found to be reversed with shape assembling process to tiny PDMS and other substrates including glasses [16]. Reversing them but also through plasma oxidizing process we not only can cascade PDMS to itself and to other potential material used in microfluidics [16].

The elasticity of PDMS is amazing and this is its quality made it

Material property	Si (single silicone)	Glass	SiO_2	PDMS	PMMA	Paryelen	polycarbonate
Thermal expansion ($x10^{-6}$ °C)	2.6	0.55	0.55	310	55	0.35	70.2
Thermal conductivity (W $cm^{-1}K^{-1}$)	1.57	0.011	0.014	0.0018	0.002	$8.4x10^{-4}$	0.002
>70%optical transmittance (nm)	>700	>350	>350	400~700	400~700	400~700	400~700
Maximum processing temp (°C)	1415	550~600	1700	~150	~100	290	~100
Bulk resistivity ($\mu ohm cm$)	$2.3x10^{11}$	$>10^{10}$	$>10^{10}$	$>10^{20}$	$>10^{20}$	$>10^{20}$	$>10^{20}$
Dielectric strength ($x10^6$ V cm^{-1})	3	5~10	2~3	2.1	0.17~0.19	2.67	0.39
Water contact angle (degree)	110	20~35	~30	~110	60~75	87	78

Where: PDMS(poly(dimethylsiloxane)), PMMA (poly methyl metha acraylate)

Table 1: Property of materials used in microfluidics device (Xunli Zhang, et al., 2006).

best choice for microfluidics along with higher permeability compared with PMMA and glass [18]. Due to its porosity at the backbone with matrix of Si-O and alkyl group covering it has some cons [12]. Among the limitations, miss matching with solvents of carbon and hydrogen, inability to perform quantitative studies owing absorption of small molecules of hydrophobic through channels wall, adsorption of biomolecules and altering solution content with water evaporation [12].

The thermoset family contains SU-8 and polyamides. With proper fabrication techniques, full 3D microfluidics device is possible from thermoset material [19]. Thermosets are characterize stability at higher temperature, optically transparent and solvent resistance. These materials also exhibit pronounced strength. The other types of materials used are hydrogels. These materials are 3D hydrophilic network of polymer chains that can span longer in water. These materials mimic the extracellular matrix due to this most of device made applied for studies in tissue engineering. Some of their properties are high permeability, high porosity, biocompatibility and lower density resulting in lower resolution compared to polymer materials used in microfluidics fabrication (Table 2) [18].

To conclude, material selection plays significant role in the success and growth of the microfluidic technology and application. Careful approach should have to be taken in selecting materials using parameters compatibility, fabrication, ease of manufacturing method application possibility, and check for material ability to allow electro-osmotic flow along required solvents.

Fabrication techniques of microfluidics devices

Fabrication techniques employed differ considering the material selected for the application. There are four major methods of manufacturing microfluidics [20]:

- Photolithography
- Hot Embossing
- Powder Blasting
- Injection molding
- Laser Manufacturing

Photolithography with chemical etching: Commonly applied for glass material based microfluidics device manufacturing [20]. The procedure goes here. On the beginning of the process, the designed structure of network prepared with appropriate computer application. The target-sized inverse of the designed network is prepared through photo reduction to have optical mask. A photographic glass of borosilicate mask covered with chromium metal with upper positive photoresist approximated 0.5 to 2 micrometer thick prepared for the network production. After the above steps and preparation, the pattern interconnection of network translated from the mask to the photoresist. Post light exposure, the developed photoresist removed, along the chromium-covering layer to clear the glass to be etched

The etching process accomplished by applying 5% NH4F and 1% HF in water at a temperature of 65°C; the product will be etch rate of 0.3-0.5 micrometer per minute. To ensure consistent availability of etchant agitation is very important. This also help for adequately removing the etching debris. The plate etchant next pass to sealing using bond to the higher layer, produced with the dame glass and involving holes predrilled for linkage between tubing of the reagent supply. The thermal bonding process supported with block weight placing quartz of non-adhering and high softening of the upper plate temperature. The above-mentioned approach is also applied to create molds used in polymer based microfluidics devices.

Hot embossing: It is one of microfluidics manufacturing technique implemented. It contains four steps. First, we will coat the substrate material with thin film polymer by spin coating or other coating mechanism. The upcoming procedure is embossing, by predetermining the necessary parameters such as packing force, temperature and holding time, we will press the mold on the pre-heated polymer film for the appropriate holding time. After the pressing, we will demold it carefully to avoid possible damage. It requires good substrate polymer adhesion. Finally, we will etch for the holes opening. Figure 1 below demonstrate the process.

Molding: Mostly applied for polymer material based microfabrication of microfluidics [21]. As the molds can be used repeatedly it saves time and cost [20]. The process detail goes here: Networks and channels of the microfluidics design on PDMS material can be easily through pouring the agent for curing and the oligomers on the surface of glass or silicone made molds. After the curing, the PDMS develop a strong block, in addition to network of channels molded on the surface of the substrate. The next step is to peel of the polymer material. Holes for fluid access created by punching across the block, and then bonded once after plasma procedure to cover made of glass sheet closing channels. Another option in closing channels to apply easy cover and clamp either from plastic or from glass made this make the polymer block to be operational liquid or air assembled component, optionally reopened. Molds preparation can follow hot embossing, casting, hot injection or photolithography is also possible.

Selective laser induced etching (SLE): SLE is new approach to manufacture a true 3D microfluidics device mostly applied transparent material (glass, sapphire and silicone) based materials [22]. It is easy two

Applications	Silicone/glass	Elastomers	Thermosets	Thermoplastics	Hydrogel	Papers
CE	Excellent	Moderate	Good	Good	N/A	N/A
Electrochemical detection	Good	Limited	Moderate	Moderate	No	Moderate
Organic synthesis	Excellent	Poor	Good	Moderate/to good	N/A	N/A
Droplet formation	Excellent	Moderate	Good	Good	N/A	N/A
PCR	Excellent	Good	Good	Good	N/A	N/A
Protein crystallization	Poor	Good	Poor	Moderate	N/A	N/A
Bio-culture	Moderate	Good	Moderate	Moderate	Excellent, 3D	Good, 3D
Cost of production	High	Medium	High	Low	Medium to high	Low
Reusability	Yes	No	Yes	Yes	No	No
Disposable device use	Expensive	Good	Expensive	Good	Hard to store	Good

CE: Capillary Electrophoresis, PCR: Polymerase Chain Reaction

Table 2: Summarize materials with possible rating in different microfluidics device fabrication (Kangning Ren et al., 2012).

(2)-step process. First laser will be focused and radiated on micrometer area where the material is transparent at the wavelength of the laser. The radiated laser attenuated by the focal spot. The attenuated energy create heat and ablate the material to form network on the material [22]. Layer by layer and line after line full 3D networked volume made available in glass for scanning. In the second step the product is taken from laser station to etching and inserted to chemical and etching begin on the surface and complete the production process by removing all the material modified during the first step [22].

Powder blasting: It a very old technic where a particle is accelerated with high pressure across a nozzle of diameter 1.5 mm toward target surface to erode the material [23]. The particle hit the surface at a speed of 290 m/s. There is a lateral movement in the process to make sure evenly surface modification mean while the target is under a mask. Figure 2 demonstrate the process.

Some of the important features of powder blasting technique include, it is low cost, can be applied to all materials having brittle nature (i.e. glass, silicone and ceramics) [23]. The rate of surface removal approximated to 25 micrometer per minute with possible enhancement through using multiple nozzles and high air pressure and amendment in powder surface flow. By their nature polymers and metal has a property to withstand powder blast due their nature applied as covering mask. As drawback, it creates a rough surface through the process [24].

Application of Microfluidics Devices in Biomedical

Microfluidics devices recent technology for the medical application that incorporated with micro size channels for the controlling, manipulation, administering and precisely localized the specific pharmaceutical drugs, *in vitro* implants and transdermal devices into the specific organs. Microfluidics devices which have its own controlling and manipulation techniques at specific location and time such controlling or triggering techniques includes temperature, time, distance, pH, magnetic field, electric field, electrochemical dissolution, telemetry and the rate of diffusion.

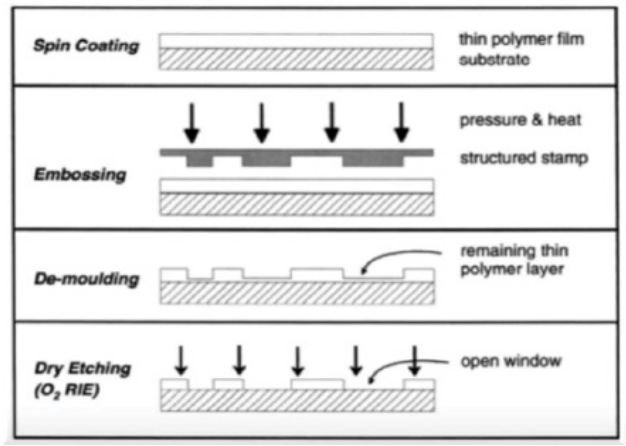

Figure 1: Hot embossing process.

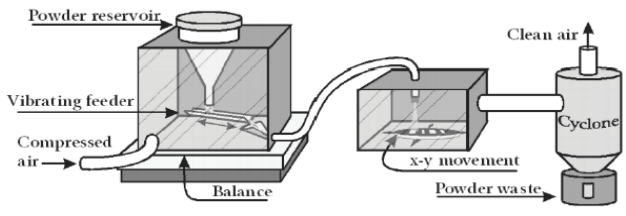

Figure 2: Schematic representation of powder blast method (Wensink et al., 2002).

Now a day the medical practice utilizes a conventional method. These conventional methods used natural ways, surgery, injection, oral delivery techniques. This method may take to be effective long time, affective neighbor tissues, miss the targets and other health problems. The Microfluidics devices reduced such health problem through accuracy, short time, short distance and administer to the precisely organs at the right time with micro size channels powerful platforms and triggers which allows controlled dosing with lower toxicity with the control windows [25]. The microfluidics devices manufacturing from biomaterials which chemically, physically biocompatible with tissues and its high conductive and high resistive corrosion. The most common materials for microfluidics devices manufacturing from metallic or polymer such as, silicon, PDMS, glass, polyester, ceramics, thermoset and thermoplastic materials and SU-8 [25]. Generally, this chapter provides a brief note enlightening the application of microfluidics in the biomedical fields and we have explained some basics application and summarized in tabular forms.

Drug delivery

Microfluidics drug delivery devices is one of the recent efficient drug delivery tools, which used for disease treatment by precisely administering a pharmaceutical medicines compound to attain therapeutic effect on disease in the human body. Drug delivery a method or the process, which administer the medicine to the specific organs through microfluidics devices to treat the disease. Conventional drug deliver through the oral delivery or injection are the most common and predominant ways or routes for pharmaceuticals drug administration. This method has its own draw backs which are non-local treatment and toxicity to healthy tissues. The development of Microfluidics drug delivery devices overcome this problem through precisely localized, with the powerful platforms which and allows can controlled dosing with lower toxicity with the control windows [24]. Herein, we focus mainly two kinds of drug delivery devices: Micro-reservoir and micro/nanofluidic devices with working principles and applications in biomedical fields

Micro-reservoir-based drug delivery systems

Micro-reservoir-based drug delivery devices is a transdermal drug delivery system which releases drug by means of triggering techniques with less order rate for maintaining constant drug levels to reduce side effects and release the drug at the right time and place [26].

Microreservoir-based drug delivery devices consists of reservoirs containing drugs, release control systems, and biodegradable polymers or metallic layers as membranes. The devices have individual or multiple drugs reservoir with the sealed which isolating them from the environment and protect from release before triggering. The biocompatible metallic or polymer layer or membrane covering on the drug reservoir is opened or degraded on command or the trigger techniques at the specific place to expose their contents to the body. The techniques of triggering of the devices with different approach, which includes devices temperature, pH, and magnetic and electric field [25].

Microreservoir-based devices have been developed from silicon and polymer based drug delivery devices which the silicon based drug

delivery devices typically have an array of cavity shape, with metallic walls on a lateral surface and the drug release achieve by different triggers, such as electrochemical dissolution, telemetry, temperature/thermal, and magnetic force whereas the polymer based drug delivery devices controlled with the different biodegradable rates of the materials used, the molecular mass, and the composition and thickness of membranes (Figure 3) [26,27].

Micro/Nano-fluidics-Based drug delivery systems

The Micro/nanofluidics-based drug delivery devices one of the drug delivery devices which delivering the drug to the specific local at micro/nano dimensions. This unique characteristic of micro/nanofluidic devices allows as controllable platforms to precisely perform and localized drug. The techniques of triggering mostly manipulated through flow diffusion [28]. The micro/Nanofluidics devices have reservoirs, channels, pumps, and valves are primary components for precise drug delivery by implanted or transdermal techniques.

The pharmaceuticals Drugs stored in drug reservoirs are precisely moved to desired locations by control parts through the micropumps and valves and release when the triggering activated where the devices reached at the target place. The applications of micro/nanofluidic devices were concentrated on drug delivery, disease therapy, microchemical reactors, diagnosis, protein and DNA separation, and cellular analysis (Figure 4) [24,29].

Biosensors diagnostic and monitoring devices

Microfluidics devices have significance application in biomedical field for the detection and sensing of Immunoassays in laboratory which found the human body such as protein detection in the biological samples [24]. Microfluidics of Point-of-care diagnostic devices have an advantage in health care for the diagnosis and detection of diseases in rapid, low cost, portability, precise response and the major aim of the microfluidics POC diagnostic is to develop a chip-based, self-containing miniaturized device that can be used to examine different analytes in complex samples [6]. The Microfluidics diagnostics and sensing detection methods for immunoarrays are based on tags that produce fluorescence, colorimetry, chemiluminescence, electrochemistry and other methods. The glucose, cholesterol, creatinine, bilirubin and others POC tests meters also with test strips with integrated with bio-receptors (enzyme, mediator) which identify the specific substance in the sample and others within the three electrode system (Working, Auxiliary and reference electrode) (Figure 5).

Cornea replacement

The microfluidics used to replace the abrasive parts of the cornea. Cornea is the transparent pars of the eye and that covers front parts of it (pupil, iris and anterior chamber). Cornea consists of five parts the epithelium, Bowman's layer, the stroma, Descemet's membrane, and the endothelium. The cornea's used for to refract, bend and focusing most of the light that enters the eye. The cornea rehabilitates and repair itself from minor abrasion however the cornea damaged totally lose its transparence leading to visual impairment [28]. The microfluidics used for the development of scaffold from collagen and hydrogen by using the techniques of bio printing are extrusion-based bio printing, laser-assisted printing, inkjet printing, and stereolithography for the 3D microfabrication technologies which allowed the reconstruction of the native microarchitecture that controls migration, differentiation, epithelial cell adhesion, and dynamic fluid flow that better mimics the physiology of the native cornea. Eye banks are unable to meet the demand and therefore an alternative source is required. Bioengineered corneal replacements can potentially overcome this shortage by providing tailored scaffolds with the inclusion of cells from the patient to minimize the risk of rejection. These substitutes can be used, not

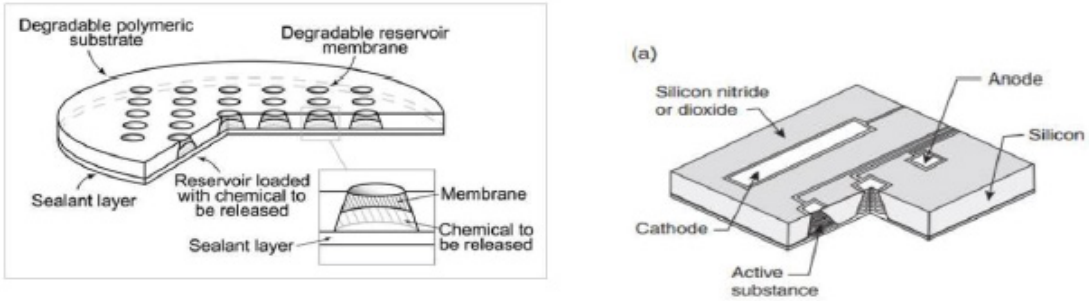

Figure 3: Schematic of polymeric and silicon microchip device.

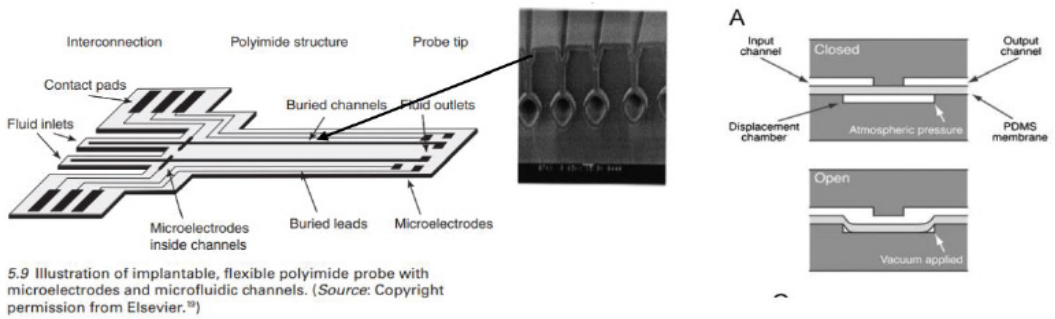

Figure 4: Schematics Micro/Nano fluidics-based drug delivery systems.

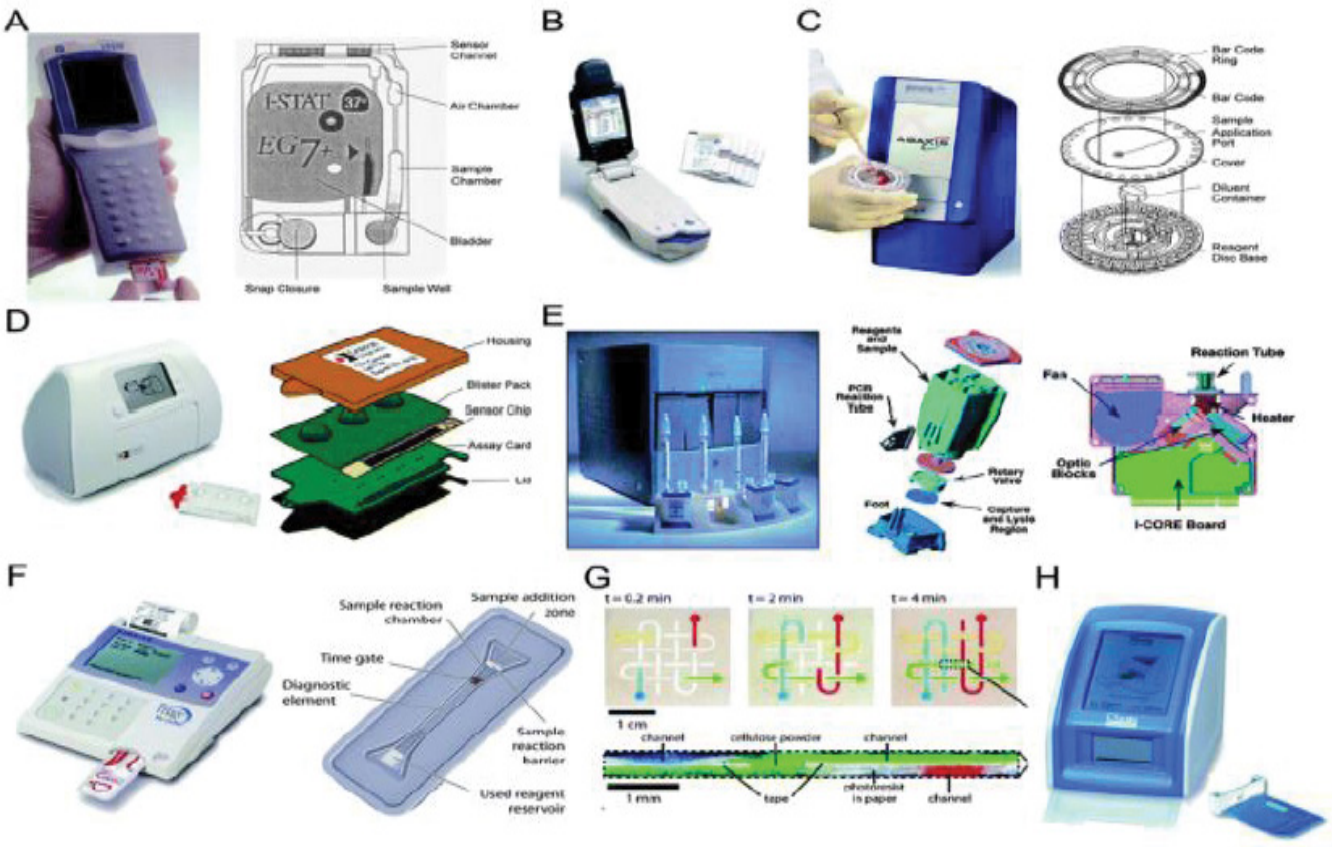

Figure 5: Different Microfluidics diagnostics and monitoring devices.

only as biomimetic corneal equivalents for use in transplantation, but also to study corneal pathologies *in vitro* (Figure 6) [6].

Retina replacement

Biomimetic stimulation of the retina with neurotransmitters, the natural agents of communication at chemical synapses, could be more effective than electrical stimulation for treating blindness from photoreceptor degenerative diseases [30] Prototype chemical synapse chip for spatially patterned neurotransmitter stimulation of the retina with artificial chemical synapse chip. (a) A cross-section of an eye showing the location in the sub retinal space of a degenerated retina where an ideal artificial synapse chip would be implanted (blue shaded region) to stimulate the neurotransmitter receptors of retinal neurons. (b) Schematic of an artificial chemical synapse chip device delivering glutamate through a microport targeting the glutamate receptors of surviving retinal neurons at a synaptic junction. (c and d) Illustrations of an artificial chemical synapse chip device positioned in the former location of the photoreceptor layer with the device microports injecting glutamate in the outer plexiform layer, mimicking the functionality of natural photoreceptors. (e) A two dimensional schematic illustrating an example pattern. stimulation with an artificial chemical synapse chip. Here, glutamate (blue dots) is injected through a select subset of a 5 × 5 array of microports of the device to stimulate the retina in a pixelated dot pattern of the letter 'E.' (Figure 7) [30].

Summary of Application

Microfluidics devices have many applications in medical industry

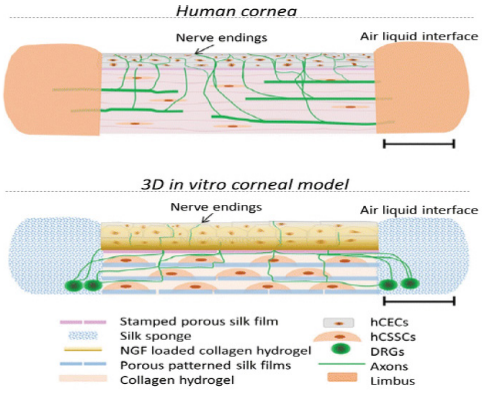

Figure 6: Microfluidics devices for cornea replacement.

for the enhanced the health care system. Those devices rapidly growth technology with its size which in micro size and micro channels for the drug delivery and implantable devices for monitoring, diagnosis and preventable services. The medical and research application of microfluidics devices includes Cardiovascular System, Respiratory system, Nervous System, Digestive+Excretory System, Endocrine System, Integumentary System, cell culturing and preparation of scaffolds, therapeutics, diagnostics and preventive system. Herewith listed the application of microfluidics platform in medical institution and research laboratories (Table 3) [31].

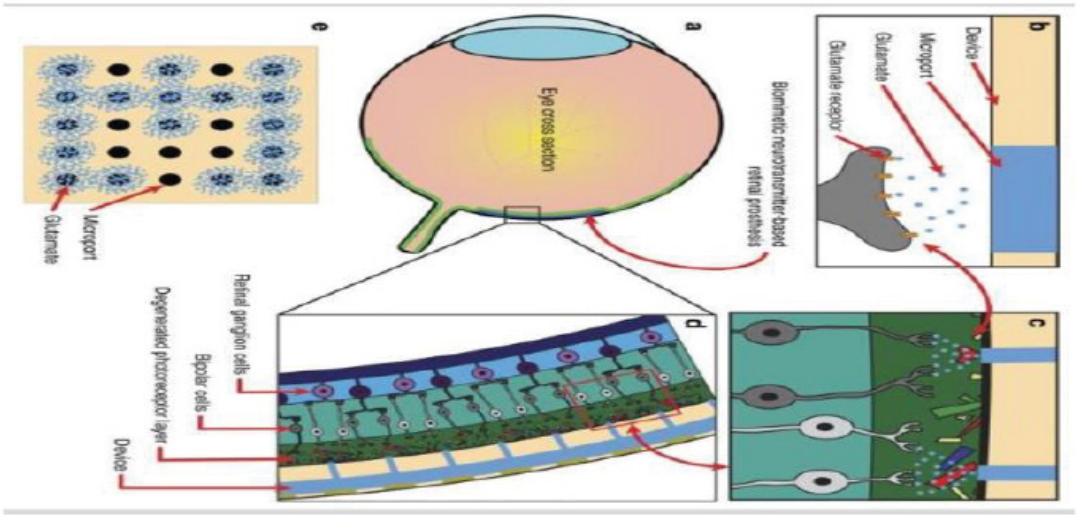

Figure 7: Microfluidics retina replacement.

Application	Microfluidics devices Platform
	Cardiovascular System
Angiogenesis studies	Dual channel chip/angiogenesis model, microfluidic tri-culture platform
Biophysical studies	Pressure attenuator + Funnel chain/cell deformability microfluidic device
	Muscular thin films
	Microfluidics + optical microscopy
	Microfluidics + ultrasound imaging system
	High-speed video microscopy in microcapillaries
Drug screening/development	Microchannel microfluidic chip
	Laminar ventricular muscle-on-a-chip
Organ/tissue structure/activity	Microfluidic cardiac cell culture model, heart-on-a-chip, artery-on-a-chip, microscale blood vessel module (μBVM) in a single microchannel device, microfluidic perfusion cell culture chip, microfluidic delivery system, microchannel biochips as vaso-occlusive processes model, perfusion microfluidic device, branched microfluidic channels
	Respiratory system
Biological barriers	Flow stretch chip
	Compartmentalized microwells in a microfluidic device
Cancer mechanisms	Microfluidics + electric fields
Cell culture	Biomimetic microfluidic airway model
Cell differentiation	3D gelatin-microbubble scaffold produced by microfluidic device
Cell migration	Dynamic transwell microfluidic system + perfusion culture, microfluidic gradient generator
Drug delivery	Microfluidics + surface acoustic wave (SAW) nebulizer
***In vivo* organ studies**	Microfluidics + single oxygenator units
Molecular mechanisms	Microfluidics + concentration gradient generator
Wound healing	Microfluidic system of converging multichannels + hydrodynamic flow focusing
	Nervous System
Axonal transport	Microchannels/microgrooves + compartmented microfluidic culture
Cell culture	Microchannels/microgrooves + compartmented microfluidic co-cultures, shear-free microfluidic gradient generator
Cell line characterization	Microfluidics + electrophoresis
	Microfluidics + quantitative reverse transcriptase polymerase chain reaction (qRT-PCR)
Cell differentiation	Microgrooves + neuronal compartment + myelination compartment microfluidic co-cultures
Cell migration	Microfluidic microgrooves + compartment to culture explants + compartment with Matrigel® to receive migrating neurons
Cellular/Molecular mechanisms	Two-compartment microfluidic culture system (neuronal compartment + myelination compartment) microfluidic co-cultures, microfluidic axon-microglia platform, axon injury micro-compression platform
	Microfluidic devices or bioreactors + ultra-performance liquid chromatography-ion mobility-mass (UPLC-IM-MS)
Drug delivery	Microfluidic + perfusion device
Drug screening/development	Microfluidic “Fish-Trap” array, gravity-induced flow + microfluidic chip
	Microfluidics + trans-endothelial electrical resistance (TEER)
Organ/tissue structure/activity	Microfluidic “Fish-Trap” array, two-compartment + microchannel microfluidic culture system

Screening / Diagnostic	Microfluidic cell sorter
Synaptic studies	Three compartment microfluidic device competition experiment, two cell culture chambers + funnel-shaped micro-channels microfluidic device
Toxicity studies	Axonal microfluidic chambers
	Microfluidics + 96-well plate
	Digestive + Excretory System
Cell culture	Biomimic hydrogel nephron
	Integrated Dynamic Cell Culture Microchip (IDCCM), Microfluidic endothelial-like barrier, dam-wall and nozzle microfluidic device, hemi-coaxial-flow channel microfluidic, dual perifusion platform
	Microfluidic bioreactor
	Microfluidic droplet-based cell encapsulation
	Multiwell culture system
	Microfluidic-multilayer device (MMD)
Cell differentiation	Microfluidic cell culture chamber/channels
	Microfluidics + qRT-PCR
Circulating tumor cells studies	Microfluidic geometrically enhanced mixing chip, Geometrically Enhanced Differential Immunocapture (GEDI) device
Drug screening/development	Gut-on-a-chip, 3D villi scaffold + microfluidic device, IDCCM
	Microfluidics + optical fiber
	Microfluidic cell culture array
	Microfluidic droplet-based cell encapsulation
	Three-dimensional microfluidic microanalytical micro-organ device (3MD)
Food analysis	Microfluidics + Fluorescence imaging
Metabolism studies	IDCCM, two-plate bioreactor, metabolomics-on-a-chip, microfluidic delivery device, two-color detection microfluidic system, multimodal islet hypoxia device
	Microfluidic bioreactor
	Microscale cell culture analogue (μCCA)
	Microfluidics-optical sensor
	Multiwell culture system
Organ-organ interaction	Integrated Insert in a Dynamic Microfluidic Platform (IIDMP), on-chip small intestine-liver coupled microfluidic network
Screening/Diagnostic	Microfluidics + surface plasmon resonance
	Microfluidics + optoelectronic sensor
	Microfluidics + optomechanical metric
Therapeutic systems	Wearable ultrafiltration units for dialysis
Toxicity studies	Metabolomics-on-a-chip, Gut-on-a-chip, IDDCM bioreactor, pharmacokinetic microfluidic perfusion system
	Kidney and kidney/liver microfluidic biochips
	Microfluidics + optical fiber
	μCCA
	Microfluidic bioreactor
	Microfluidic human kidney proximal tubule-on-a-chip device
	MMD
	Multiwell culture system
	Endocrine System
Cancer mechanisms	Microfluidic co-culture model, chemokine gradient + 3D culture device
Fertilization	Motile spermatozoa sorter + microfluidic chip, microfluidic device mimicking female reproductive tract
Metabolism studies	Microfluidics + resonant waveguide grating (RWG) sensor
Monitoring	Microfluidics + electrochemical sensor
Screening and diagnostic	Blood plasma separation microfluidic chip
	Microfluidics + optical sensor
	Microfluidics + liquid chromatography-mass spectrometry
	Microfluidics + potentiostat
	Microfluidics + electrochemical sensor
	Digital microfluidics
	Integumentary System
Biological barriers	Stable gel/liquid interface microfluidic chip
Cell differentiation	Pillar array microfluidic device based on cell surface markers
Cell migration	3D matrices microfluidic device
Screening and diagnostic	Microfluidics + conductometric sensor
	Microfluidics + potentiometric sensor
Skin repair	Microfluidic wound-healing model + wound dressing screening

Table 3: Summary of microfluidics application in biomedical fields.

Conclusion

Recent advances of microfluidics devices application in biomedical fields were rapidly growth with controlled mechanisms, accuracy, precisely localized, Nano/micro size scale and administered with short path into the specific organs. Microfluidics devices in biomedical research centers, hospital and health institution contributing in health care system and with powerful devices. These devices used in medical monitoring, diagnosis, therapies and drug delivery of specific analytes, implantable and assisted devices with integration of micro/Nano fabrication multiples channels of biomaterials, which is biocompatible platforms to regenerate and rehabilitate physiological and pathological conditions of complex tissues and organs.

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