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Review

Microfluidics and personalized medicine towards diagnostic precision and treatment efficacy

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Abstract

Microfluidics is a science that flows at the microscopic scale. However, it is also mature technology that has already been applied to everyday technology such as e-readers, inkjet printers, and lab-on-a-chip devices that can shrink a whole laboratory down to a few square inches. Microfluidics can be applied to personalized medicine in addition to everyday technology. Treatment for individuals is adjusted to their specific characteristics through personalized medicine. Based on this biomarkers and drug screening are used for maximizing efficiency and reducing adverse effects. The need for well-regulated, sustainable, and detailed methods is constantly needed to reduce reagent use and improve overall healthcare outcomes. Here we show the development of microfluidic technologies to advance personalized medicine by analyzing microRNAs, and other biomarkers through high-throughput screening, integrating advanced data analytics to match a particular treatment to a patient's unique genetic profile and response.

Keywords

Bionsensor, microfluidics, drug discovery, biomarkers, personalized medicine

1. Introduction

Microfluidic devices can attain flow rates as low as 1 picoliter per minute, which is one trillionth of a liter and about one million times smaller than a drop of water. The small scale of channels and the ability to finely tune the fluid dynamic within the microfluidic system allows for precision in the flow control of microfluidic devices. This type of precision enables microfluidic tools to improve health outcomes for over 4 million people around the world by allowing fast and accurate disease testing in different regions. Microfluidics studies the behavior of fluids at the micro to nanometer scale. It can miniaturize the work of a whole lab onto a microfluidic chip less than a few inches big. Microfluidic devices consist of intricately etched microchannels connected to the external environment via openings for fluid injection and expulsion.

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These systems use Quake valves and a pressure control mechanism to manage the flow of fluids within the channels [1]. While being no more than an inch in size, microfluidic devices have several advantages over real-scale systems like being able to analyze samples and reagents with less volume. This makes it more cost-effective, decreasing experiment time while having a small footprint.

During the 1990s, microfluidics led to the development of lab-on-a-chip devices for medical diagnosis. A lab-on-a-chip is a small device that combines high-resolution laboratory procedures for fluid transport, mixing, and analysis into a system that fits on a chip [2]. This technology is used in high throughput screening where lab-on-a-chip systems can check large amounts of drug formulations. By doing this, the drug discovery process speeds up. Lab on a chip is famously used in diabetes management since this device can monitor glucose for daily blood sugar checks. Organ-on-a-chip, another common microfluidic device used, duplicates the operation of a living organ inside a chip and allows for research mimicking human physiology [3]. This allows researchers to study organ-specific responses to various stimuli, drugs, or diseases in a controlled setting. This chip contains microfluidic channels that mimic the organs, blood vessels and tissues. Within these channels, living cells and tissues from the organ are cultured. Organ-on-a-chip is most used in drug development and testing. These include when the device simulates how drugs are absorbed, distributed, and metabolized in the body. As a result, the drug's behavior in the body can be understood. Treatment and care for individuals are adjusted to their specific characteristics through personalized medicine. This approach considers factors like genetics, environmental, and lifestyle differences to optimize treatment and improve health outcomes [4]. Genetic testing is an early part of personalized medicine to identify any genetic mutations or variations that may affect the patient [5]. This is called genetic profiling. Doctors can prescribe drugs based on everyone's results and microfluidics plays a role in this part of personalized medicine. Microfluidics enhances personalized medicine through rapid analysis and efficient screening in high throughput testing by analyzing multiple biological samples or biomarkers from a single patient and quickly screening for genetic mutations, protein levels, or other indicators of disease. Through the multiple ways microfluidics is improved in personalized medicine, it produces cost-effective solutions by using smaller volumes of reagents and through the miniaturization of diagnostic processes, microfluidics can reduce the cost of testing and analysis. In this review we discuss the progression of microfluidics in personalized medicine with applications in specialization fields of organ-on-chip, lab-on-chip and point of care molecular diagnostics.

2. Fundamentals of Microfluidics

The basic principles of microfluidics involve the integration of principles of fluid dynamics, chemistry, physics, and engineering. Microfluidics fabricate devices that handle very small volumes of fluid with high precision. Fundamentals of microfluidics involve several applications, production methods, control mechanisms, and fluid dynamics on a microscopic size scale [6]. Laminar flow is one of the most basic concepts in microfluidics. It underlies a flow regime called the Microscale of Fluid Dynamics, where smooth and orderly fluid flow takes place [7]. In fact, because the channels in microfluidic systems are so narrow, the flow is mostly laminar. When viscous forces, which are important at this microscale, outweigh the inertial forces, there develops laminar flow. The result of this is a very small exchange of fluids between the layers because they run parallel. Laminar flow must be understood when one is developing devices that could employ it. The development of microfluidic devices usually uses techniques adopted from fabrication in the semiconductor industry. The important fabrication techniques include a process known as photolithography, where the microfluidic channels are defined on a substrate, normally silicon or glass, through the creation of a patterned mask on a photosensitive material [8]. Soft lithography is a flexible process that makes use of PDMS and other elastomeric polymers. First, using photolithography, a master mold is fabricated with the desired channel geometry, over which PDMS is poured [9]. When cured, the PDMS is removed to reveal the channel network, which can be bonded to other surfaces to form a complete device. Etching Microchannels can be etched into substrates such as silicon and glass by wet and dry techniques. While in dry etching, plasma is used to achieve the correct dimension of channels, wet etching relies on chemical solutions for material removal [10]. Both these techniques enable the fabrication of complex microfluidic networks and structures in an easier way to create devices with accurate and repeatable properties. Mechanism fluid control in microfluidic devices could be properly achieved through a variety of ways. Stress-Related circulation is the method that relies on pressure differences to advance the fluid flow within the channels [11]. The fluid could be managed with very high precision by changing the applied pressure at the input and output. This technique is being highly utilized in applications that require constant flow rates. Electrokinetic flow includes electric fields that apply forces on the charged species in a fluid and develop electrokinetic forces. These forces are harnessed in methods such as electrophoresis and electroosmosis to pump fluids and particles. Biomolecules-based separation and analysis processes would highly benefit from the use of this technique. Vascular Forces are capillary action that uses the surface tension available that naturally makes the fluid rise to the top or flow through the minute channels. This is a common approach in passive microfluidic systems, where the movement of the fluid is tightly controlled by channel design alone [12].

3. Applications in Personalized Medicine

Human tissues and organs are complex and are in an ordered arrangement of multiple cells that carry out their function. To support the 3D arrangement of target organs, microfluidic technology is required. Organ-on-a-chip is a multidisciplinary system with technological integration from stem cell biology to tissue engineering. The goal of organ-on-a-chip is within precise simulation of the physio/pathophysiological-relevant microenvironment of specific human tissues or organs through regulating key conditions. The lung in the human body has important functions like respiratory regulation and immunity similar to an organ of the human respiratory system [13]. The lung has two zones known as the conducting zone and the respiratory zone. Air exchanges between the external environment and internal vessel systems occur through the continuous movement of the alveolar sac located in the bronchioles after flowing through the conducting airways [14]. The lung's blood-air barrier has been replicated by microfluidic organ-on-a-chip systems by implementing dynamic perfusion and mechanical movement. In early studies, a lung-on-a-chip designed by Huh *et al.* used a flexible membrane to simulate breathing, with human lung cells cultured on either side [13]. This model successfully replicated conditions like pulmonary edema by introducing specific proteins. Other models have explored respiratory diseases, such as cystic fibrosis and asthma, by recreating disease-specific conditions and responses, including the effects of SARS-CoV-2 on lung inflammation and barrier disruption. Recent advancements include chips with biological membranes that better simulate the lung's natural environment and functionality compared to traditional materials like PDMS. For instance, a chip with a collagen-elastin membrane supports more accurate cell behavior and mimics the spatial configuration of alveoli. New models of bronchioles have also been created to study complex interactions, such as infections, in a more realistic setting [15].

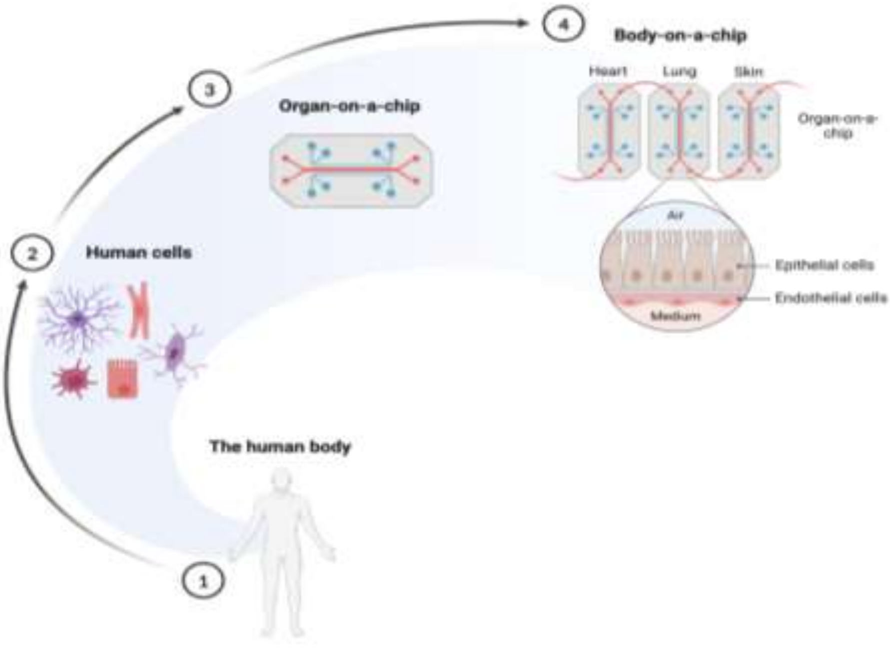

Figure 1. *(1-2) Illustration of the human body consists of multiple systems working together to maintain homeostasis, while each cell plays unique functions. (3-4) Microfluidics allows for the study of complex physiological system-system interactions and diseases in high-throughput controlled devices.*

As shown in Table 1, droplet based microfluidics allows for the creation of small sized droplets with controlled flow rates to flow inside of microfluidic devices in a continuous motion, usually suspended in fluid [16]. Oftentimes, the fluid used is water or oil [17]. The process of creating droplets requires a great amount of precision to ensure that all droplets maintain a consistent size; some techniques that have been successfully deployed include cross-flowing (T-junction), flow focusing and co-flowing [18]. The integration of droplet-based technology with microfluidics primarily serves the purpose of multiplexing different fluidic operations on the same chip. Droplet microfluidics allows researchers to work with small sample size volumes and give precise control over experiments [19]. Some of the popular applications in personalized medicine include controlled release systems where we can have a timed release of droplets, isolate rare and targeted cells in single cell analysis, and incorporate the use of organ-on-chip to accelerate drug discovery [20]. Digital microfluidics employs microfluidic technology to control microdroplets for the purpose of high-precision fluid handling. It generates and manipulates mono-disperse drops that could be in a volume from femto-liters to nano-liters within an immiscible phase [20]. This technique benefits from its microscale nature and allows for the integration of sample preparation, analysis, and detection at high throughput with precise control. It has many advantages over bulk reactions, such as reduced reaction times, savings regarding samples and reagents, high multiplexing, and high sensitivity [19]. The main advantage of digital microfluidics compared to conventional techniques is the large area-surface-to-volume relation of the microfluidics, which can shorten reaction times in drug development [21]. Droplet-based microfluidic devices are also capable of multiplex assays in drug screening. Digital microfluidics enables the precise control and manipulation of small biological samples on-chip for eventual diagnostics and treatment tailored to a patient's specific needs [22]. Organ-on-a-chip is a microengineering biomimetic system that functionally and structurally reflects that of human tissue [23]. In a miniaturized platform, techniques from biomaterial technology, cell biology, and engineering combine. Organ-on-a-chip can be produced at a low budget and can be tested with a wide range of drug concentrations on the effect of medicine [24]. The results of a new drug in development could be tested countless times without any fear of financial ruin. There would also not be any of the ethical issues that go along with animal testing-one of many growing societal concerns today. Organ-on-a-chip can be applied in dermal diffusion testing for skin-on-a-chip to evaluate how chemicals penetrate through the skin [23]. A more in-lab accurate representation of human organs and tissues allows for the enhancement of drug efficiency testing through more precise evaluations of drugs affecting specific tissues. Organ-on-a-chip represents experimental platforms for systematic functional investigation of the action of drugs and disease processes and hence provides insight into possible therapeutic mechanisms and side effects [25]. On the other hand, organoid-on-a-chip technology helps make drug testing better by using cells from real patients to create models that closely mimic diseases. By combining organoids, which are tiny versions of organs, with chips that recreate the body's environment, scientists can test how different people might react to new drugs. This approach helps personalize medicine by predicting side effects and finding the best treatments for individual patients [26]. The fabrication of paper-based microfluidics is through patterning paper with hydrophobic barriers to present hydrophilic channels and zones [27]. Like traditional microfluidic devices made from polymers, paper-based microfluidic devices are portable and process small-volume fluids, with the ability to execute multiplexed assays. Paper-based microfluidics can be easily incorporated with sensors to allow real-time biomarker detection to facilitate rapid diagnosis. [28]. Paper-based microfluidics have a low cost which makes them accessible to wide usage on both clinical and field levels, which may bridge gaps in health access for the underprivileged. Due to the rapid nature of these devices, paper-based microfluidic devices enable timely and efficient analysis, which is necessary for prompt medical interventions and decisions. Paper-based microfluidics make diagnostics accessible at a relatively lower cost due to their inexpensive materials and straightforward methods of production, hence expanding access to health in poor resource settings [29]. Fast biomarker detection and point-of-care tests ensure speed in results and this makes medical diagnosis and treatment quicker and more effective [30]. Gut-on-a-chip technology is used in personalized medicine to create small, human-like models of the gut for studying diseases and testing new treatments. This helps researchers understand how different patients might react to drugs or therapies, allowing for more tailored and effective medical care [31]. The human gut is vital for digesting food, absorbing nutrients, and supporting the immune system, with important structures like crypts and villi that help with these functions. Researchers have created "gut-on-a-chip" models to simulate the gut's barrier and environment [32]. These models often use two main methods: mechanical actuation to mimic gut movement and scaffolds like collagen hydrogels to create villi-like structures [33]. They also recreate the gut's oxygen gradient and microbiome by controlling oxygen levels and growing bacteria alongside gut cells. To test the gut barrier's function, scientists use techniques like measuring molecular permeability with dyes and checking trans-epithelial/endothelial electrical resistance (TEER). Some advanced chips even have semitransparent electrodes for real-time monitoring, helping to study gut health and disease more effectively. Heart-on-a-chip technology is used in personalized medicine to study and address heart diseases like myocardial necrosis and heart failure [34]. These chips simulate the heart's biological mechanisms and functions, such as cardiomyocyte contraction and electromechanical loading, to evaluate how different treatments affect heart cells. For example, by mimicking systolic and diastolic phases and using advanced sensors to measure contractile force and cell behavior, researchers can test drug responses and enhance cardiac regeneration. This approach helps in developing personalized treatments by providing insights into how individual patients' hearts might react to various therapies, improving drug discovery and treatment outcomes

Reference	Microfluidic Technique	Description	Application in Personalized Medicine	Key Advantages
[35]	Droplet-based microfluidics	Manipulation of discrete droplets	Single-cell analysis, High-throughput screening	High throughput, Encapsulation of rare cells
[36]	Digital microfluidics	Microfluidics technology controls tiny droplets for precise fluid handling applications.	Digital microfluidics enables precise manipulation of biological samples, facilitating personalized diagnostics and tailored treatment solutions	Precise control, high throughput, flexible assays, and reduced reagent use
[25]	Organ-on-a-chip	Systems containing engineered or natural miniature tissues grown inside microfluidic chips to better mimic human physiology	Improves drug efficacy testing, and targeted therapies, and used as experimental systems to systematically study the functional effects of varying levels of specific dietary factors.	Precise simulation, reduced animal use, real-time analysis
[27]	Paper-based microfluidics	Devices made out of paper, or other porous membranes, that wick fluids by capillary action	Affordable diagnostics, rapid biomarker detection, point-of-care testing	Integration with sensors for real-time biomarker detection, affordable, rapid

Table 1. *Microfluidic platforms and their applications in personalized medicine*

3.1. Diagnostics and Biomarker Discovery

Personalized medicine is highly dependent upon biomarkers, specific analytes that can be used to enhance diagnosis to help predict likely treatment responses and guide treatment choices. MicroRNAs were discovered in 1993 and have been the focus of intense study. miRNAs are sample noncoding RNAs and only have about 22 nucleotides long cleaved from larger precursor molecules [37]. Humans express approximately 2,500 miRNAs, which play important roles in cell activity [38]. Their main role is to regulate gene expression by binding to messenger RNAs and inhibiting translation thereby influencing gene activity. To understand how genetic changes affect health and disease these molecules are very necessary. Microfluidics has altered the field of biomarker discovery by offering accurate control over fluid handling and allowing high-throughput analyses [39]. Since microfluidic devices have a small size, they can analyze minute volumes of fluid, which is useful for the analysis of rare biomarkers that could exist in very low quantities. Biomarker detection is made more sensitive and specific using microfluidic devices because complex biological tests can be carried out on a small scale [40]. These devices many times combine multiple functions into a single chip, which lets researchers conduct different types of analyses simultaneously. Microfluidic systems can replicate the physiological environment of cells or tissues, which allows for more accurate data on biomarker interactions. This capability increases the understanding of how biomarkers behave in real biological contexts, leading to more precise diagnostic tools. Traditional methods require bigger sample volumes and time-consuming processes but microfluidic devices can achieve these results faster with less material [41]. This efficiently increases the biomarker discovery process. In microfluidics, it is important to analyze biomarkers fast. The ability to analyze biomarkers rapidly and with a strong accuracy rate is a significant advantage of microfluidics [42]. Traditional methods often require larger sample volumes and more time-consuming processes, whereas microfluidic devices can achieve the same results more quickly and with less material. This efficiency not only accelerates the biomarker discovery process but also makes it feasible to administer high-throughput screening. This was because many potential biomarkers can be tested in a smaller period.

3.2. Drug Development and Screening

Personalized medicine changes the way we use and develop drugs today. Individualized treatments are implemented to fit everyone's characteristics through a more personalized approach. Genes and their functions are the subject of genomics. By using genomics, personalized medicine can determine a person's response to particular medications based on their genetic makeup [43]. A certain gene has to be looked at and then scientists can predict how well a drug will work and if it might have side effects for a certain person. CYP2C19, for example, affects how people process the blood clot prevention drug clopidogrel [44]. It is possible for doctors to determine whether clopidogrel will work for a patient by testing for this gene or if a different medication is needed. Additionally, biomarker indicators can help in diagnosing disease and help in treatment decisions [45]. They are important in personal medicine because they can help figure out which treatment will be the most effective for specific patients based on their unique biological markers. Traditional drug screening uses testing different compounds to see if they might work. Personalized medicine makes this more advanced which allows for this process to be faster and more accurate. High throughput screening lets scientists test large batches of drugs faster [46]. By using cells from different patients, researchers can see how different people will react to a new drug. Additionally, by using artificial intelligence, personalized medicine relies on collecting a lot of data through patient recording. This data can be analyzed with artificial intelligence to identify patterns and predict how different treatments will affect patients [47]. Artificial intelligence can, for example, suggest treatment options based on a patient's genetic information and medical history.

3.3. Treatment Monitoring

Treatment monitoring can be done through different techniques within microfluidics. One is microfluidic-based nano biosensors. Nano-biosensors provide healthcare professionals with the right information needed to manage patient healthcare to deliver point-of-care solutions [48]. Microfluidic nano biosensors use ideas from nanotechnology with microscale fluid flow for identifying and quantifying molecules. These sensors are typically made of antibodies or other biomolecules and nanomaterials to be able to help detect targeted molecules [49]. An advantage of microfluidic-based nano biosensors is their ability to offer real-time biomarker monitoring at minimal biomolecule concentrations with high sensitivity and specificity [50]. This reduces the possibility of false positives and negatives during the testing process. Whether it be saliva or another type of liquid, nano biosensors can detect biomarkers in noninvasive samples. Nano-biosensors, over time, have become extremely versatile as they can detect many analytes simultaneously and relate to other technologies like microfluidic pumps and valves. Because of this, sensors can used in a variety of areas for healthcare towards monitoring electrical signals and neuro-emotional responses [51] [52]. A more recent development includes the multi-organ-on-a-chip. This was developed for monitoring the brain metastasis process in real-time. The metastasis process is when cancer cells leave the original tumor and through the blood system, they form a new tumor in a different organ or tissue of the body [53]. This could be harmful and thus is important to keep track of. The monitoring of the metastasis process through multi-organ-on-a-chip is unique because it is not a technique that can be achieved by other developed models. The multi-organ-on-chip consists of a functional blood-brain barrier (BBB), which is a layer of cells in the brain that keeps harmful substances away [54]. The multi-organ-on-a-chip is support for someone who is going through cancer and to keep track of the metastasis process, microfluidics is a sensible way to do so. Ovarian cancer is another type of cancer where this kind of monitoring can be utilized [55]. Like all cancers, an unusual cell starts reproducing without control and forms a tumor. It is tough to notice this in the early stages as symptoms show up easily, but microfluidics may have the advantage over conventional methods to identify ovarian cancer. Using microfluidic technology with biosensors is more accurate compared to traditional platforms in detecting cancer biomarkers. In a study, microfluidic systems were developed by magnetic graphene nanosheets to electrically monitor a specific enzyme in real-time [56]. This was done by realizing copper ions that resulted from enzymatic hydrolysis. One other such work has described the construction of a photoelectrochemical sensing system, using reduced graphene oxide nanohybrids for signal-on detection of prostate-specific antigens, coupled with a magnetic microfluidic device [57]. In all, there is still an urgent need for accelerated diagnosis with high accuracy, and this is a point where microfluidic systems intervene.

Microfluidic devices have engineered fluid flow confined to small objects and are becoming a popular platform in cancer research, monitoring, and diagnosis [3].

4. Conclusion

4.1. Limitations and Challenges

Several limitations and challenges are in current research, one being scalability. This is when traditional microfluidic devices manufactured using soft lithography struggle to scale up for high throughput applications [6]. These devices are good in laboratory settings for small-scale experiments however translating these innovations into larger-scale production is still a challenge. Technical hurdles would have to be dealt with for the intricacies involved in keeping precise control over fluid dynamics at a larger scale such as ultrasonic technology [58]. Microfluidic systems are designed for specific applications which result in complex devices that are difficult to integrate with other technologies. This specialization can limit the versatility of microfluidics compared to conventional methods which are more common. Integrating microfluidic devices with other analytical tools would need major modifications which would disrupt practical implementation. Conventional methods can benefit from materials techniques whereas microfluidic devices are occasionally limited by properties of polymers in their creation. An example of this is the choice of material such as polydimethylsiloxane can limit optical transparency, chemical compatibility, and mechanical durability. For experiments in microfluidics to be done they must be replicated however this is difficult because of how sensitive microfluidic devices are to variations in fabrication processes and conditions of the environment [59]. Microfluidic devices can show significant variability between different batches which affects the reliability of results. Bulk sequencing is analyzing genetic material from a mixed population of cells, however, it cannot provide insights into the gene expression of each cell because of cellular variability, which is important for understanding complex biological systems [60]. Additionally, cost is an important factor in research since developing advanced microfluidic systems can be expensive. Conventional methods like bulk sequencing have become less expensive since they require fewer samples and less complicated technology, however, the cost of microfluidic technology can be prohibitive which limits its accessibility and adoption [61].

4.2. Future Outlook

Improvements can be made to scalability through developing new fabrication methods like high-resolution 3D printing which will allow microfluidic devices to be created at larger scales while maintaining precision [62]. Improved scalability allows production and high-throughput screening, making microfluidic systems more applicable in industrial settings [63]. Alongside this, a model-based systems engineering approach towards development would further allow for a streamlined methodology for development [64]. Microfluidic devices can be specialized and hard to integrate with other analytical tools, limiting their versatility thus integrated systems can create an integrated lab-on-a-chip platform that combines multiple functionalities into one device to reduce complex modifications [65]. This allows for easier integration of a broader range of applications and more comprehensive analyses which would make microfluidic devices stronger in different fields of research. The use of materials like polydimethylsiloxane (PDMS) can limit optical transparency and other necessary tools, however, the use of composite materials that combine the advantages of different polymers can improve device performance [66]. This will improve the functionality including increased durability, optical clarity, and chemical resistance. Variability in fabrication processes and environmental conditions affects the reproducibility of microfluidic devices [6]. This issue can be improved upon by implementing automated and controlled fabrication processes to reduce variability and allow consistent quality across batches. Using standard protocols can help make sure that devices are made and tested the same way every time, which improves how consistent and reliable the results are. Enhanced reproducibility ensures more reliable and consistent experimental results, making microfluidic devices more dependable for research and clinical applications [41]. Better reproducibility means that experiments will produce more reliable and consistent results. This makes microfluidic devices more trustworthy for research and medical use.

Author Contributions

S.T., S.V., K.D., literature review, writing – original draft and writing; S.V., K.D., conceptualization, writing - review & editing.

Conflicts of Interest

The authors declare no competing financial interests or conflicts of interest.

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