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Review Article

RECENT INNOVATIONS IN MICROFABRICATION TECHNIQUES FOR ENHANCED MICROFLUIDIC CHIP PERFORMANCE IN DRUG DEVELOPMENT

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ABSTRACT

An example of a mobile laboratory is microfluidic chip technology or lab-on-a-chip. It is one of the great breakthroughs in the pharmaceutical industry as it allows flexibility in controlling experiment conditions, minimizing sample and reagent waste, and allowing high-throughput screening. Microfluidics has roots in molecular analysis, microelectronics, biodefense, and even molecular biology; likewise, gas-phase chromatography and capillary electrophoresis are ancestors for it. Determining the use of this equipment in laboratories leads to automation, miniaturization of procedures, precision and uncertainty in drug creation, and repeatable experiments, which enhances the accuracy of results. Its merits are the performance of computerized simulation of organs, where it enhances the drug screen, toxicity testing, personalized medicine, and pharmacokinetics, which leads to the testing of thousands of candidate drugs being tested at once. Its performance is excellent; however, it cannot be denied that it has a disadvantage, which is in designing the chip and integrating it with the already existing system. It has yet to integrate widely used markers for patient samples and other markers to improve point-of-care diagnostics that aim to use the patient's sample to work on to change the structure of future studies in the pharmaceutical industry.

Keywords: Lab-on-a-chip, High-throughput screening, Microelectronics, Microfluidic technology, Molecular biology, Drug delivery systems, Point-of-care diagnostics, Biomarkers

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INTRODUCTION

The pharmaceutical industry is ever-changing and requires more sophisticated, accurate, and cost-effective solutions for drug development and testing. Of all the emerging technologies the industry has access to, microfluidic chip technology is arguably the most exciting. Microfluidic chips, also known as "lab-on-a-chip," combine different reagent functions of a laboratory onto a single chip capable of processing minute fluid volumes. Technology has the power to revolutionize pharmaceutical analysis through unparalleled accuracy in control of experimental parameters, minimized consumption of both sample and reagents and enhanced throughput [1, 2]. The four key areas of microfluidics are molecular analysis, biodefense, molecular biology and microelectronics. Microfluidics originated from microanalytical technologies, including Gas-Phase Chromatography (GPC) [1], High-Pressure Liquid Chromatography (HPLC), and Capillary Electrophoresis (CE) [3]. High efficiency of the above techniques, especially when incorporated with laser optical detection, achieved high resolution and sensitivity with the use of little sample volume. This success paved the way to the development of compact and adaptable formats for the majority of the chemical and biochemical applications [4-6].

The second impetus was the post-Cold War need to respond to chemical and biological threats. The US Department of Defense Advanced Research Projects Agency (DARPA) funded research in the 1990s to create field-deployable microfluidic systems for their detection, significantly advancing the academic microfluidic technology [7]. Molecular biology provided the third thrust. The genomics revolution in the 1980s and the development of high-throughput DNA sequencing required higher throughput, sensitivity, and resolution analytical tools. Microfluidics offered solutions to these issues [8, 9].

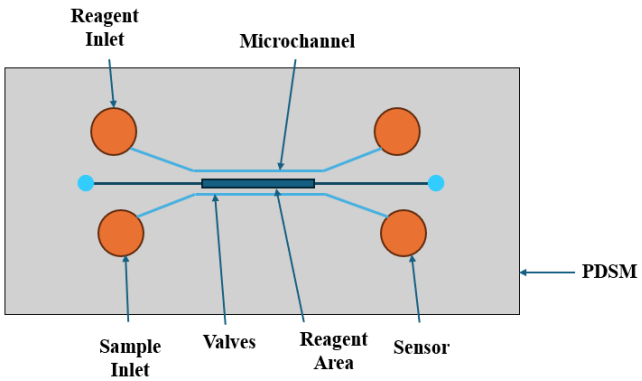

Fig. 1: Diagrammatic representation of a microfluidic chip

Finally, microelectronics added value by transferring photolithography and related technologies from silicon microelectronics and Micro-Electro-Mechanical Systems (MEMS) to microfluidics [7]. Silicon and glass were employed in early

microfluidic systems, but these were subsequently replaced primarily by plastics based on economic and practical reasons. Silicon, while expensive and UV and visible light opaque, was not ideally suited to standard optical detection techniques. Elastomers were more frequently employed for making components such as pumps and valves, as these are more in line with living cells [10-13].

Microfluidic chips, or "lab-on-a-chip" devices, have come a long way since their beginning. During the 1960s, the development started with microanalytical techniques such as gas-phase chromatography, high-pressure liquid chromatography, and capillary electrophoresis. The 1970s witnessed the introduction of miniaturized gas chromatograph analyzers using silicon wafers, whereas silicon micromachining technology paved the way for new microvalves and micropumps in the 1980s. The 1990s heralded the use of Polydimethylsiloxane (PDMS) in fabricating microfluidic chips and silicon-based microfluidic analysis chips. The 2000s experienced the emergence of soft lithography for PDMS, which supported the miniaturization and automation of lab processes. More recent literature on 2023-2024 emphasizes improvements in microfluidic-based vasculatures on chips for mimicking human blood vessel networks to be used in drug delivery and metabolism research.

Moreover, lab-on-a-chip technologies have advanced accessibility, usability, and manufacturability for enhancing clinical diagnostics and translational research. Some milestones include developing integrated circuits, photolithography, and organ-on-a-chip models with physiological mimicry of drug testing and disease modelling. Prospects include enhancing chip robustness, growing applications towards drug delivery systems and point-of-care diagnostics, and creating innovative fabrication methods to deal with the present limitations. Microfluidic technology continues to transform pharmaceutical research and development, streamlining drug discovery and making it more effective.

Microfluidic chips are very powerful tools for drug Research and Development (R and D). These tiny devices manipulate fluids with remarkable precision at the microscopic scale, enabling scientists to miniaturize and automate complex lab processes. All of this tech doesn't only time accelerates the process of finding new drugs-it also allows for more consistent and reliable experiments, which will help us get even more accurate results. Microfluidic technology in conjunction with pharmaceutical analysis, has revealed new avenues for drug screening, toxicity testing, pharmacokinetic analysis, and personalized medicine [14, 15].

One of the key advantages of microfluidic chips is that they can conduct high-throughput screening. Since common drug screening methods are usually tedious and time-consuming, the small number of compounds that can be screened suggests that they are extremely limited. Microfluidic chips, on the other hand, have the potential to screen an ensemble of drug candidates simultaneously, significantly increasing the throughput of screening effective therapeutics. The high-throughput nature of such an assay has enabled vast compound libraries to be screened for biological activity in the early drug development phase [16, 17].

Microfluidic chips also play a fundamental role in drug metabolism and pharmacokinetics studies, in addition to high-throughput screening instrumentation. Microfluidic chips can simulate human organs' microenvironment and, thus, allow studying the drug absorption, distribution, metabolism, and excretion processes in the human body. These data are pivotal in determining the safety and efficacy profiles of new pharmacological agents. Microfluidic chips will also enable the creation of organ-on-a-chip systems with the ability to mimic the physiological response that is unique to human organs. These models are better representations of human biological systems than traditional cell culture or animal-based study designs, thus offering greater predictive sensitivity for preclinical research [18-21].

Toxicity screening is an important application of microfluidic technology to drug evaluation. Microfluidic devices' capability to quantify the toxicological action of drug candidates on various cell types lessens dependence on animal testing and yields more meaningful data on human biological processes. In addition to being more ethical, this method strengthens the validity of toxicity testing. Microfluidic chips can design complex drug delivery systems, such as nanoparticles and liposomes, which can be accurately designed and delivered directly to tissue or cells to improve treatment efficiency and minimize side effects [22-24]. Microfluidic chips are also transforming point-of-care diagnosis. The handheld, portable chips can quickly test patient samples for a set of biomarkers, facilitating quick and precise diagnosis of disease. This feature is especially important in low-resource settings where well-equipped laboratory space is limited. By providing early diagnostic information, microfluidic chips can enhance patient management and treatment outcomes [25-28].

Microfluidic chips with organ-on-a-chip technology have been presented as better alternatives to animal testing in pharmaceutical studies. Microfluidic chips can recreate human organs and organ function in a controlled microenvironment, allowing for more reliable and human-relevant models for drug toxicity and efficacy studies. Microfluidic chips can culture the living organs in this physiological state while allowing researchers to study drug absorption, distribution, metabolism, and, consequently in, excretion from the body. This alternative method raises ethical considerations and experimental accuracy since animal models are often not accurate predictors of human response. However, there are challenges in validating microfluidic-toxicity-based assays in response to regulations. Reproducibility and robustness are key concerns when moving ass or toxicity work to the marketplace. It is critical to make sure that a microfluidic toxicity assay would perform the same across laboratories and experiments would yield the same results regardless of the assay performance routine. The regulatory body is expected should provide extensive validation data because we need to be confident these assays will predict human outcomes consistently. For regulatory approval, microfluidic-based assays will need to go through significant validation to show that the results will be reliable and predictable. This requires showing the ability to reproducibly obtain results between labs and reproducibility related to predicting human responses to drugs with consistent outcomes. As regulatory agencies such as the Food and Drug Administration (FDA) begin to acknowledge these New Approaches Methodologies (NAMs) they are starting the journey to incorporate them into the process of drug development. The FDA Modernization Act 2.0 even allows the exploration of non-animal-based approaches within investigational new drug applications as they begin to modernize drug development and testing for more humane approaches. Ultimately, microfluidic chips allow for fewer animal testing efforts by allowing for more accurate human representation for models of drug toxicity and efficacy. The clinical data generated from these models will have an increasing role in the regulatory process and, subsequently, the drug development process, while there will continue to be inconsistencies reaching regulatory approval with these assays, the ongoing developments and supportive legislation with regulatory agencies will enable greater acceptance of microfluidic technology for pharmaceutical research.

Microfluidic chip fabrication techniques vary widely, each with its own set of advantages and limitations. Here's a comparative analysis of some prominent methods:

In short, the application of microfluidic chip technology to pharmaceutical analysis is a significant advance toward more efficient and effective procedures in drug development. Herein, we review microfluidic chips for multi-purpose applications in pharmaceutical analysis and their potential to revolutionize the industry. In exploring the recent advancements and potential future of microfluidic technology, we will strive to give an overarching view of the contribution of microfluidic technology to the history of pharmaceutical R and D.

Drug delivery system

They provide well-controlled synthesis and microscale drug carrier delivery ability; thus, microfluidic chip-based drug delivery systems have revolutionized drug delivery systems [29]. These chips enable the production of nanoparticles and microparticles with uniform size and shape, which are crucial for effective drug delivery. Microfluidic technologies can alter the dynamics of fluids to create high efficiency of encapsulation and targeted delivery, hence lessening drug loss and

degradation [1, 29-32]. Incorporation of biosensors with real-time monitoring inside microfluidic systems facilitates fine-tuning release profiles of drugs for increased therapeutic performance and decreased adverse effects [26]. Besides, microfluidic chips allow the development of multifunctional drug carriers. Inorganic substances, polymers, and lipids are introduced into the drug carriers for achieving controlled release and targeted delivery. Microfluidic technology offers high-throughput screening and rapid prototyping, which speed up the formulation and design of new drug formulations and delivery systems [33, 34]. Ongoing research attempts to deal with problems such as scalability and integrating with the existing manufacturing process by advancing microfabrication techniques and introducing artificial intelligence in the optimization of the process [35]. Microfluidic chips present a completely novel means of drug delivery systems which allow precise control, efficiency and scalability of delivery, which can improve patient results and advance medicine. These are the ways that drug delivery is achieved with the use of microfluidic chips:

Nanoparticle and microparticle fabrication

Microfluidic chips fabricate nanoparticles and microparticles for drug encapsulation. Those particles can release drugs at controlled rates that reach tissues or cells [22, 36]. Control over microfluidic flows is applied to fabricate uniform-sized and shape particles that are crucial to stable drug delivery [37].

Fabrication techniques

Several methods of particle fabrication have been performed in microfluidics, such as droplet, continuous flow, and segmented flow techniques. Droplet-based microfluidics creates uniform droplets serving as tiny reactors for creating particles [38, 39]. Continuous flow microfluidics enables the constant production of particles by continuously blending reactants within microchannels. Segmented flow techniques employ immiscible fluids to form distinct reaction zones, providing better control over particle formation [40-42].

Table 1: Different fabrication techniques, their advantages and limitations

Fabrication technique	Advantages	Limitations
Soft lithography	-Flexibility in design	-Durability issues with PDMS
	-Cost-effective	-Limited resolution
	-Biocompatibility	
CNC milling	-High precision	-Higher initial setup costs
	-Material versatility	-Complexity in fabricating intricate designs
3D printing	-Design flexibility	-Lower resolution
	-Customization	-Limited printable materials
Laser ablation	-High precision	-Undesirable thermal effects
	-Rapid fabrication	-High equipment cost
Hot embossing	-High throughput	-Time-consuming setup
	-Material compatibility	-Resolution dependent on master mold quality
Paper-based microfluidics	-Extremely low-cost	-Limited to simpler assays
	-Portability	-Less durable

Table 2: Properties of various microfluidic device materials [90]

Property	Silicon/Glass	Elastomer	Thermoset	Thermoplastics
Young's Modulus	130-180/50-90	~0.0005	2.0-2.7	1.4-4.1
Microfabrication	Photolithography	Casting	Casting polymerization	Thermo-modling
Smallest Channel dimension	<100 nm	<1 µm	<100 nm	~100 nm
Multilayer Channels	Hard	Easy	Easy	Easy
Thermos ability	Very High	Medium	High	Medium
Solvent Capability	Very High	Low	High	Moderate
Oxygen Permeability	<0.01	~500	0.03-1	0.05-5
Optical Transparency	No/High	High	High	Medium to High

Encapsulation efficiency

Microfluidics technology improves drug encapsulation efficiency into carriers. Compared to traditional methods, these microscale channels allow for efficient mixing and reaction conditions to produce higher capture efficiencies in the encapsulated structures to ensure a great deal of the drug reaches its target site [43-45]. The chips allow for well-controlled fluid dynamics in the microscale, producing high encapsulation efficiency into uniform and monodispersed particles. Varying microchannel geometries and multiphase fluid flow rates permit microfluidic devices to fabricate particles of the same size and shape, which is crucial for drug-delivery efficacy. The encapsulation efficiencies gained through microfluidic procedures frequently outperform those through traditional bulk processes in that the confined settings reduce drug losses and degradation [46]. This is particularly advantageous when developing nanoparticle-based drug delivery systems since keeping therapeutic agents stable and available for absorption is of high importance. Along with this, microfluidic chips open room for the incorporation of diverse materials such as polymers, lipids, and inorganic substances, thus creating multifunctional nanoparticles to effect targeted drug delivery and controlled release [47]. The deliberate tuning of the physicochemical properties of such particles adds to the therapeutic potency and minimizes adverse side effects. In addition to that, microfluidic platforms promote high-throughput screening and quick prototyping in accelerating the development of new drug formulations and delivery strategies [46]. Yet, despite the many advantages, scalability and integration with current manufacturing systems remain challenges. New family-based parallelized microfluidic systems and the use of artificial intelligence for optimized particle synthesis are being researched to deal with these problems. Overall, microfluidic chips present improved techniques of drug encapsulation efficiency in drug delivery systems and serve as a platform to explore modern-day therapies with maximized effects and diminished side effects, indeed, an amply promising perspective [48].

Microfluidic chips have transformed High-Throughput Screening (HTS) in drug discovery by allowing rapid screening of thousands of compounds while dramatically increasing precision. Microfluidic chips process very small fluid volumes with precise control of experimental conditions, increased assay sensitivity and decreased reagent requirements. Compared to the traditional approach (96-or 384-well plates), which screens thousands of compounds per day, microfluidic HTS platforms can screen tens of thousands of compounds daily, mostly due to smaller assay volumes and

automated systems. This 16-fold increase in throughput is made possible by the reduced assay volumes, which affords the luxury of time for chemical and protein libraries and reduces the overall demand on costly reagents. Smaller assay volumes allow for greater sensitivity when studying the interactions between compounds and test systems via the confinement of interactions on a small scale, ultimately producing data with better accuracy and repeatability. Ultimately, real-world applications of microfluidic chips, such as perfusion flow platforms and droplet-based systems, have shown they can effectively facilitate drug discovery by dismantling the bottlenecks in pharmaceutical research. These platforms allow for detailed information on the specificity of compounds and pharmacological activity throughout primary screening [16].

Continuous production

Microfluidic chips do great revolutions in continuous production by enabling real-time control of fluid dynamics at the micro-scale. This enables continuous, efficient manufacture of particles and compounds of exact size and shape, with applications in pharma, diagnostics, and materials science. With microfluidic devices, continuous-flow techniques allow the continuous production of high-quality material at a steady rate to ensure uniform quality and maximum output. That minimizes the waste generated and the long post-processing typically required, thus being more cost-and eco-friendly compared to the traditional batch counterparts [49, 50]. Furthermore, microfluidic systems with sensing and online automated controls provide real-time monitoring and tuning of the parameters affecting production, leading to improved reliability and efficiency. Another solution for the scalability problem is parallelization in terms of microfluidic channels for ramping up production, which is suitable for industrial applications. However, it also has several challenges, such as integrating with existing manufacturing processes and retrofitting a microfluidic system to be robust on a larger scale. The research conducted to date is directed at overcoming these challenges by building on advances in micro-manufacturing and enhancing it by embedding artificial intelligence technology for optimized process control. To highlight, microfluidic chips are a step toward, if not necessarily the solution, to continuous production with high precision, efficiency, and scalability in industrial applications [51, 52].

Integration with diagnostic tools

Microfluidic chips have rearranged continuous production processes by enhancing fluid dynamics control at the microscale level, thereby manufacturing particles and compounds of similar size and shape. These characteristics are important in pharmaceuticals, diagnostics, and material science. By using microfluidics in continuous-flow technologies, production rates are maintained at continuous levels, ensuring uniform quality at high output. This lessens wastage and the need for extensive post-processing, thus cheaper and more environmentally friendly in comparison to traditional batch methods [49, 50]. Also, integration of sensors and automation into microfluidic systems allows real-time monitoring and correction of production parameters, increasing the reliability and efficiency of the process. Besides, addressing scalability issues for onward industrial applications through upwards parallelization of microfluidic channels has provided the promise of successful scaling up of production processes. Unfortunately, despite their advantages, there are issues regarding interfacing current implementation methods into manufacturing processes and building reliable, large-scale microfluidic systems. Ongoing research seeks to overcome these barriers through one or multiple ways by modernizing microfabrication methods and coupling artificial intelligence for optimized process control. Microfluidic chips have a lot of promise in terms of continuous production, offering precision, efficiency, and scalability for many kinds of industrial applications [51, 52].

The implementation of qualification tools into microfluidic chips has considerably accelerated the phase of medical diagnostics, mainly toward rapid, accurate, and cost-effective fulfillment. Also known as lab-on-chip devices, microfluidic chips allow for miniaturization and automation in the optimization of lab processes, performing different task operations in one chip [53]. By the incorporation of biosensors, optical detectors, and electrochemical sensors, these chips can highly sensitively and specifically further detect and quantify certain biomarkers. Such integration makes it suitable for real-time monitoring and analysis of biological samples, which reduces diagnosis time while enabling point-of-care testing. Controlling the flow of fluids in precise as well as clear microfluidic channels is such that it allows perfect mixing, good separation, and good reactions of the analytes so as to enhance reliability in the diagnostic results [53, 54]. In addition, microfluidic systems use small sample volumes, thereby creating a different kind of diagnosis that is less invasive and friendly to the patients. The ability to fit different modalities onto a single chip also creates the potential for multiplexed assays, enabling the detection of many biomarkers in a single run. With several challenges, including scalability and integration with existing health infrastructure, researchers are keen to find a way around these bottlenecks. In summary, the integration of diagnostic tools into microfluidic chips presents a game-changing avenue in medical diagnostics with promises of making them more efficient, accurate, and available [55, 56].

Microfluidic pumps and valves

Microfluidic pumps and valves are core building blocks that take control of fluids at the microscale. Therefore, the open and directed flow of the fluids is key to chemical synthesis, biological assays, and medical diagnosis. A microfluidic pump that has peristaltic, diaphragm and electroosmotic principles can produce a continuous or pulsatile flow, ensuring constant and reliable delivery of fluid. Valves allow precise on-off control and flow modulation through solenoid, pneumatic, and elastomeric types, thereby increasing versatility and function in microfluidic devices [57, 58]. By integrating these pumps and valves with microfluidic systems, it is possible to automate complex processes needing little manual intervention, increasing throughput. The miniaturized nature of these components allows for their embedding into portable and point-of-care devices, bringing advanced medical diagnosis within reach. Although there has been logic to challenge the integration of microfluidic knowledge with existing technologies, research is still fostered to support improvements concerning performance, reliability, and cost as far as microfluidic pumps and valves are concerned. Microfluidic pumps, valves, and chips, in summary, are core to any other research and development that works within the purview of microfluidics [57, 59, 60].

In a nutshell, microfluidic chips represent a very flexible and efficient platform from which the next generation of drug delivery systems can be constructed, allowing for extremely accurate tuning of the drug form, encapsulation, or release.

Case studies on microfluidic chip applications in pharmaceutical R and D

Jiksak bioengineering: ALS drug development

Microfluidic chips have shown great promise in drug development as evidenced by numerous real-world examples. One of the more notable applications has been to advance pharmaceutical development in Amyotrophic Lateral Sclerosis (ALS) by Jiksak Bioengineering (Jiksak Bioengineering). Jiksak Bioengineering is using microfluidic chips to create neurons by mimicking the body's environment and growing nerve tissue in three-dimensional space. In providing an organ-on-a-chip model it provides a much more useful approach to an accurate testing model for potential treatments and has significantly advanced drug development for ALS [61]. Another application of microfluidic chips is through droplet-based microfluidics that have been advanced for drug screening and drug formulation applications. This system can provide precise control and solid manipulation of small droplets, allowing for high-throughput screening and more efficient testing of multiple drug candidates.

Microfluidic chips can also be used to simulate human organ environments to study drug metabolism and the pharmacokinetics effect. By simulating the organ environment, animal testing can become less relied upon and provide human-centric results (more pertinent and relevant for research and development efforts), which can create more accurate outcomes for drug development [1]. Overall, these case study examples demonstrate the ever-increasing ways that the microfluidic chip can change pharmaceutical research and development through efficiencies in drug discovery.

Personalized medicine

Microfluidics chip promotes personalized medicine, as it features accurate and efficient solutions for individualized treatment for a patient. The chips allow complex processes in laboratories to miniaturize and automated, performing fast analysis on biological samples from patients, which are patient-oriented. It is also through the use of biosensors and online monitoring that microfluidic devices can carry out the detection and measurement of biomarker activities with high sensitivity, providing the required information for a personalized treatment plan [61]. This offers the potential to use customized drug formulations and delivery systems based on patients' genetic and biochemical profiles. There are, however, some other microfluidic chips that enhance high-throughput screening, thus allowing testing of multiple drug candidates and combinations within a fraction of the time to find the right treatment for each patient [62]. On the plus side, it also assists the production of point-of-care diagnostic devices, taking personalized medicine closer to everyone while minimizing diagnosis time and adjustments to the treatment. Challenges such as scalability and integration into existing health systems might be tackled with ongoing research that aims to develop microfabrication technology while simultaneously integrating AI for optimized process control. Simply put, microfluidic chips are transforming personalized medicine with high precision, efficiency, and adaptability, such as improving patient outcomes and healthcare advancement [55, 63].

AI-driven microfluidic platforms further enhance personalized medicine by tailoring patient-specific drug treatments. These platforms integrate microfluidic technology with artificial intelligence to analyze complex data sets and predict optimal therapeutic strategies. For instance, AI can process high-throughput data from microfluidic assays to determine the most effective drug combinations and dosages for individual patients. In Chronic Myeloid Leukaemia (CML) treatment, AI-driven microfluidic systems have been used to select the most suitable BCR: ABL1 Tyrosine Kinase Inhibitors (TKIs) based on patient-specific biological and genetic factors. This integration allows for real-time monitoring and adjustment of treatment plans, improving therapeutic outcomes and minimizing adverse effects.

Personalized customization of medical treatment for the unique characteristics of each patient is gaining prominence and prominence in recent times. Microfluidic chips, also known as lab-on-a-chip devices, represent perhaps the most important technological development in the personalization of medicine today. Designed to allow precise control and manipulation of small volumes of fluid, these chips will be used to engineer personalized treatment strategies mirroring an individual's unique genetic and biochemical profile [21, 61]. This is how microfluidic chips are affecting changes in personalized medicine.

Table 3: Comparison of microfluidic approaches vs. conventional methodologies

Aspect	Microfluidic approaches	Conventional methodologies
Precision	High precision in isolating and analyzing single cells	Bulk analysis of cell populations, less precise
Sensitivity	Enhanced sensitivity due to miniaturization and integration of biosensors	Lower sensitivity, often requiring larger sample volumes
Throughput	High-throughput screening capabilities, processing thousands of samples simultaneously	Limited throughput, slower processing times
Cost	Reduced reagent consumption and operational costs	Higher reagent consumption, more expensive
Personalization	Tailored treatments based on individual genetic profiles and cellular responses	Generalized treatments, less personalized
Regulatory approval	Requires extensive validation and standardization for regulatory approval	Established methodologies with existing regulatory frameworks

Genetic analysis and mutation detection

Microfluidic chips have revolutionized genetic analysis and mutation discovery via accurate, rapid, and efficient processing of biological samples in very high numbers. With these chips, complex procedures that are normally encountered in laboratories are intricate and automated, thus providing the ability to analyze more than one or many genetic markers at once. High-sensitivity and high-specificity genetic mutation detection and quantification with microfluidic devices can be achieved when made by integrating biosensing with real-time monitoring. This function is of great importance in cancer diagnosis because early detection of oncogenic mutations leads to the best-informed treatment and consequently to patient welfare. However, the relevant mixing, separation, and amplification of nucleic acids all occur at a microscale through the control of fluid dynamics, which serves to optimize the accuracy and reliability of genetic analyses [64, 65]. Furthermore, microfluidic chips allow for the realization of point-of-care diagnostic tools, which enhance the accessibility of genetic testing and reduce the turnaround time for results. Although scalability and integration into the current healthcare systems are significant issues, investigations that intend to tackle such complications still receive ongoing support via the enhancement of microfabrication technologies and the integration of artificial intelligence, enabling optimized process management shortly. Very briefly put, microfluidic chips offer an emerging methodology to genetic testing and mutation detection, combining high precision, efficiency, and versatility to enrich diagnosis capabilities while enhancing personalized medicine [61, 66, 67].

Drug Testing with Organoids: The area of organoid-based drug testing saw a major leap through the development of microfluidic-enabled chips, allowing precise control over the microenvironment and rapid, high-throughput drug screening. Such chips help to perform complex lab processes in miniature and more automated ways, leading to efficient organoid culture and manipulation, given that organoids are three-dimensional cell structures that replicate the architecture and function of human organs. Microfluidic devices, with their integrated biosensors and real-time monitoring, may now assess the drug candidate-induced effects on organoids with high specificity and sensitivity. Such assessments are extremely valuable when determining the oncological efficacy and toxicity of the treatment by visualizing the cellular responses in a controllable and reproducible manner. In addition, drug-testing capacity in microfluidics is augmented by the formation and maintenance of concentration gradients in the channels that mimic *in vivo* environments [61, 68, 69]. Moreover, microfluidic chips can be instrumental to personalized medicine by allowing the testing of patient-derived organoids mapping individual decisions to treatment. Meanwhile, there are specific challenges, just like those of scalabilities to the modes and emulations in existing drug developments; further research would stand against such barriers by developing microfabrication techniques with artificial intelligence for inside purposes to initiate further control [69, 70]. To summarize, microfluidic chips provide a transformative approach to organoid-based drug testing, allowing for greatness in precision, efficiency, and versatility-imaging factually new aspects of drug discovery and development.

Single-cell analysis

Microfluidic chips have allowed for single-cell analysis precise and rapid high-throughput processing of single cells. In general, this type of small lab work allows the automation of such miniaturization of isolation, manipulation, and analysis of single cells, which is resolved. By integrating the powerful response sensitivity and specificity in cellular analysis and quantification of response with microfluidic devices, along with biosensors and real-time

monitoring, the method could achieve ultra-sensitive responses to various types of cells. This field presents a vast number of questions of relevance in a broad scope regarding cellular heterogeneity related to cancer, immunology, and developmental biology [16]. With microscale fluid dynamics, efficient mixing, separation, and amplification of cellular components can be achieved, which further enhances the accuracy and reliability of single-cell analyses. Also, microfluidic chips enable high-throughput screening, which allows thousands of individual cells to be analysed simultaneously, in turn expediting the search for new biomarkers and therapeutic targets [71, 72]. Some major challenges include scalability and integration into existing lab workflows, but research is underway to overcome these hurdles, focusing on the improvement of microfabrication technologies and integrating artificial intelligence for optimized process control. Microfluidic chips could truly revolutionize the field of single-cell analysis with high precision, efficiency, flexibility, and insights into cellular biology and biomedical research [33, 72, 73].

Point-of-care diagnostics

Point-of-care diagnostics (POCD) with microfluidic devices have taken a massive leap into medical diagnostics and have paved the way for fast, accurate, and cheap testing at the location of the patient. They are also termed lab-on-a-chip devices, as they put together the multitude of laboratory functions onto one chip, by means of microchannels that deal with a small volume of fluid. This innovation allows detection of a wide variety of biomarkers and pathogens with almost total accuracy and sensitivity for a much shorter timeframe than that required by conventional lab methodology. Recent improvements in the incorporation of biosensors into Microfluidic (MF) chips have greatly improved real-time diagnostics. MF with biosensors incorporate the sensitivity and specificity of biosensors with fluidic regulation and miniaturization that MF provides to allow rapid, accurate, and cost-effective analysis of clinical samples at the point of care. Significant advances which may occur in the future will include highly sensitive electrochemical and optical (bio)sensors that can detect low levels of biomarker(s), novel materials aimed at improved stability and biocompatibility and inexpensive, speedily automated processing of samples. The process miniaturization and automation are enhancing the diagnostic procedures' efficiency, thereby making them possible to function credibly in resource-limited environments. Applications of microfluidic POCD include glucose monitoring, infectious disease diagnosis, and cancer biomarker testing. In essence, these chips could bring immediate results that make it possible to make timely clinical decisions, improving patient outcomes while at the same time lowering healthcare costs. Continuous innovations in microfluidics are widening the horizons and promising broader horizons to personalized medicine and global health [74-76].

Microfluidic chips have been successfully used in cancer diagnostics, particularly in liquid biopsy applications. These chips can isolate and analyze Circulating tumor cells (CTCs) from blood samples, providing a non-invasive method for cancer detection and monitoring. The integration of biosensors enhances the detection of specific cancer biomarkers, improving the accuracy and reliability of the diagnosis [77, 78].

One of the greatest hurdles facing the mass production of lab-on-chip diagnostics is the scalability of production. Manufacturing methods such as photolithography and soft lithography, while reliable and accurate techniques are not necessarily affordable for high volume. While 3D printing, injection modelling, etc., can potentially be more efficient, these still require additional optimization steps to achieve sufficient precision and reproducibility. Moreover, the overall costs of materials and fabrication can be substantial, decreasing the chances of lab-on-chip devices becoming affordable [79-81]. This has led individuals to seek low-cost materials while simplifying fabrication as much as possible, while maintaining device quality. Furthermore, as many lab-on-chip diagnostics can have automated components that replace the actions (auxiliary equipment) of operating these diagnostics, this would also help lower operational costs. For microfluidic-based diagnostics to obtain commercial approval, they must also undergo rigorous validation standards to ensure reliability and validity. The regulations for doing this can be lengthy and expensive, acting as a barrier against the rapid commercialization of new designs. Collaborating with regulatory boards and creating standardized processes for testing and commercialization will expedite the production of new designs [82].

Microfluidic immunoassay

Microfluidic immunoassays are an important leap in diagnostics as an attractive platform for the detection of a wide array of biomarkers that is compact and cost-effective and has great sensitivity. Lab-on-chip devices use nanoliters of microchannels to push tiny volumes, producing fast and accurate immunoassay procedures that used to be confined to a larger area in a lab. By combining microfluidics with immunoassays, it should be possible to couple specific and sensitive detection of pathogens through antigen and antibody quantification using appropriate immunoassays to effect early diagnosis. This is of much use at a point of care, allowing for a rapid and accurate test that would facilitate vital interventions for treatment. Applications of microfluidic immunoassays indeed range from the detection of infectious diseases through cancer diagnostics to chronic disease monitoring. These systems are further cumulatively integrated with fluorescent, chemiluminescent, and electrochemical detection methods. In addition to the above-mentioned, it saves costs and reduces waste because of low consumption of samples and reagents, which is an advantage in all respects, both economically and environmentally. As research advances and enhances microfluidic immunoassays, the further fitting to incorporate these systems into wearables and smart technologies merely expands, thus showcasing a boon to reorienting personalized medicine and real-time health monitoring. This combination enhances patient outcomes with timely medical interventions that, in turn, reduce the pooled expenditure for health by reducing visits to clinical practice [83, 84].

The uses of microfluidic chips are opening wide, easily supported by wearable technology, hence allowing great strides to be made in chronic disease management, fitness monitoring, and remotely monitoring patients. This area of research and development further promises to revolutionize health and wellness, allowing for more personalized healthcare that is affordable and efficient.

EGFR and lung cancer

Microfluidic chips for the detection and analysis of EGFR mutations in lung cancer signify a great leap for personalized medicine [85]. Usually, mutations in non-small cell lung cancer and its enabling mutation is Adenocarcinoma; the mutations of EGFR are associated with the initiation and progression of the disease. These microfluidic chips provide a compact and efficient platform for an accurate and fast analysis of these mutations, also referred to as lab-on-a-chip devices. Using microchannels to manipulate small volumes of fluid, they are sensitive enough to identify mutated EGFR, providing early diagnosis and treatment. This is especially useful for point-of-care applications where rapid and accurate results may impact clinical decisions. The combination of the chips to advance detection systems-such as fluorescence and electrochemical techniques-greatly enhances their diagnostic performance [86]. As the research in this field advances, the integrated possibilities of microfluidic technology with wearable devices and smart technologies are growing, which could drastically improve the way health can be monitored and treated. To sum up, the introduction of microfluidic chips for EGFR mutation analysis presents a tremendous leap in the diagnosis of lung cancer and proves to be a significant tool for communication to improve patient outcomes and global health.

DISCUSSION

Microfluidics is leading the way toward personalized medicine, producing innovative mechanisms for tailoring treatments to each patient. With their genetic analysis capability, organoid-based drug testing, single-cell analysis, high-throughput screening, point-of-care diagnostics integration with wearable devices, and advanced drug delivery systems, microfluidic technologies are transforming the collection of care. Not only do these advancements enhance the efficacy and safety of treatments, but they also open the door towards a more personalized and patient-centric approach to medicine. These chips consist basically of a network of tiny channels developed in a material substrate such as glass, silicon, or polymers

that allow targeted provision and manipulation of fluids at the microscale. For their pharmaceutical capability, microfluidic chips have several types of attractive features. One of the main benefits of microfluidic chips is minimized usage of reagents and samples. Traditional pharmaceutical processes generally employ very high volumes of sometimes expensive computed reagents, but microfluidic systems take on the least activity, therefore yielding a great economy on the reagents. In addition to limiting reagent waste and thus being environmentally friendly, techniques of reduction allow these systems to effect rapid reactions and analyses [84].

Scaling up a microfluidic system is compounded by the considerations required in transitioning from prototype to full-scale production. Fabrication methods, such as photolithography and soft lithography, are well established but can be costly when full-scale production is required. Other processes, such as 3D printing and injection moulding, are being shown to address the issues related to microfluidic devices but still require optimization to enable scale, precision, and reproducibility. The use of glass for prototyping may also restrict transition to full-scale production, as polymeric materials can be used for transition to full production more easily in many instances. Continuing to deliver consistent performance and quality in large batch sizes of microfluidic devices is a significant barrier to scaling efforts [86, 87]. Establishing analytic, clinical, and scientific validity will be necessary for regulatory compliance of microfluidic systems and is a complex and time-intensive process. The absence of specific guidance and standardized considerations for microfluidics adds to this complexity [100]. Regulatory processes generally outline expectations of manufacturing to validate the process to predict human outcomes reliably and safely while also validating efficacy [88]. This process usually requires testing and comparison to established methods, and is expensive and slow in getting new technology into use. AI and automation will change the way microfluidic technology is applied. AI-driven microfluidic platform will have the capabilities to process complex data sets, enabling predictions on appropriate therapeutic approaches that will improve precision and efficiency in diagnostics and treatment. For example, AI can analyze high-throughput data results from microfluidic assays to determine the most effective drug combinations and doses that are best for individual patients. Automation of microfluidic systems allows real-time monitoring and modulation of experimental parameters, thereby improving reproducibility and reducing human error. More specifically, these advancements are expected to allow quicker drug discovery, personalized medicine and point-of-care diagnostics [89].

Another considerable advantage is the precision and control offered by microfluidic chips. The microscale environment permits precise manipulation of fluids, leading to meticulous control of reaction conditions. In particular, it is very useful in nanoparticle formulation and drug delivery systems, wherein the particle sizes and their distribution could either assure or impair the efficacy of treatment and safety level. The microfluidic chips can generate extremely uniform particles, a near impossibility with any conventional methods, ensuring consistency in drug delivery and experimental reproducibility [85]. Besides, microfluidic chips allow the integration of multiple laboratory functions into one single device. This integration, named "lab-on-a-chip", enables different procedures like mixing, separation, and detection to take place simultaneously. Thereby, processes save time and minimize the risk of contamination and human error due to a reduced requirement for manual intervention. The small form factor rotationally opens take-away point-of-care tests and on-site drug analysis when working in isolated areas or limited-resource settings.

Future lines of research should involve: Firstly, improving fabrication methods by exploring and optimizing scalable methods, such as 3D printing and injection modelling, which will improve accuracy and reproducibility, and investigating the use of inexpensive, biocompatible materials that are appropriate for mass production. Secondly, establishing standardization and regulation with collaborations with governing bodies for unique guidelines and standardized evaluation for microfluidics devices and by providing strong validation methods to show reliability and predictive capability for microfluidic-based assays.

Thirdly, there is a need for increased integration of artificial intelligence and automation but working to enhance algorithms for AI to allow for data analyses and decision-making capability in real-time, especially in closed-loop microfluidic systems, and developing automated systems for sample processing, data collection, and data analysis to improve efficiency and reduce human errors [89]. Fourthly, expanded applications should include exploring new developments of microfluidic technology applications, including in environmental monitoring, synthetic biology, and drug delivery systems, as well as developing modular microfluidics systems that can be easily modified and deployed for unique applications. Finally, collaboration and interdisciplinary research work will be essential for continued growth in looking for ways to facilitate collaboration between engineers, biologists, chemists, and data scientists to provide an environment conducive to innovation in the microfluidics technologies and interdisciplinary research to help address some of the many challenges in developing and applying microfluidics systems.

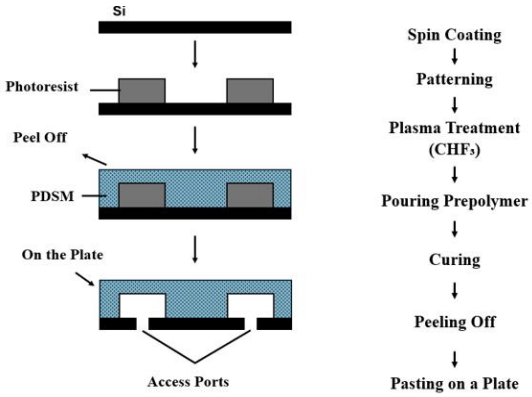

Fig. 2: Fabrication process of PDMS microchip [90]

Table 4: Comprehensive list of patents on microfluidic chip technology

Patent number	Patent holder	Date	Title	Reference
US20080003142A1	Darren l *et al.*	2008-01-03	Microfluidic devices	[91]
US10675619B2	Gottfried R *et al.*	2020-06-09	Method for manufacturing a microfluidic device	[92]
US11187224B2	Zheng X *et al.*	2021-11-30	Microfluidic chip	[93]
US11458474B2	Joshua S *et al.*	2022-10-04	Microfluidic chips with one or more vias	[94]
US11759782B2	Tiina M *et al.*	2023-09-19	Microfluidic chip and a method for the manufacture of a microfluidic chip	[95]
US20210113974A1	Euan R *et al.*	2024-03-26	Continuous flow microfluidic system	[96]

CONCLUSION

The exceptional advantage of microfluidic chips over others, from the point of view of the pharmaceutical industry, includes but is not limited to low reagent consumption, high accuracy, and the capability to incorporate several laboratory functions into one device, which would in turn facilitate drug discovery and development processes, enhance consistency in drug formulation, and also provide possibilities for point-of-care testing. Nevertheless, they pose major hurdles mostly due to complications in their design and fabrication, trouble of scale-up processes, and their ever-difficult integration into existing workflows. However, the viability of microfluidics in ushering pharmaceutical R and D forward gives a certain promise. Therefore, further microfluidic design and fabrication improvements-with special emphasis on addressing scale-up and practical integration problems-will make a strong difference in further fulfilling the promises of this technology in the pharmaceutical setting.

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AUTHORS CONTRIBUTIONS

Anakana Roy: Conceptualization, Data curation, Methodology, Writing–original draft. Ankana Roy, Gundawar Ravi: Investigation, Methodology, Writing–review and editing. Gundawar Ravi: Conceptualization, Data curation, Resources, Supervision, Visualization, Writing–review and editing. Muddukrishna BS: Formal analysis, Investigation, Supervision, Visualization. Riyaz Ali M. Osmani: Investigation, Methodology, Writing–review and editing. SG Vasantharaju: Formal analysis, Investigation, Resources, Review and editing.

CONFLICTS OF INTERESTS

The authors declare no conflict of interest

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