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REVIEW

Biomedical devices and microfluidics: development of lab-on-a-chip systems, biosensors and diagnostic devices with applications in clinical and point-of-care settings

Dispositivos biomédicos y microfluídica: avances en sistemas de laboratorio en chip, biosensores y diagnóstico en entornos clínicos y de punto de atención

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ABSTRACT

The convergence of biomedical devices and microfluidics is revolutionizing diagnosis and treatment in the healthcare sector, offering faster, more accurate, and more accessible solutions. Microfluidics, which manipulates fluids at nanometer and micrometer scales, leverages principles such as laminar flow and diffusion to enable the development of miniaturized systems. Labs-on-a-Chip (LOC) are the embodiment of this symbiosis. These devices integrate multiple laboratory functions into a single platform, utilizing manufacturing techniques such as photolithography and 3D printing. Their impact is palpable in the rapid detection of pathogens, the diagnosis of chronic diseases and cancer, drug discovery, and personalized medicine, facilitating point-of-care (POC) testing with minimal sample volumes and reduced costs. The integration of biosensors (optical, electrochemical, nucleic acid-based) into microfluidic platforms enhances biomarker detection with high sensitivity and specificity. This translates into earlier diagnoses and continuous monitoring. Although these advances promise to transform healthcare, significant challenges remain. Production scalability, cost reduction, regulatory harmonization, and the need for biocompatible materials are crucial hurdles. However, future trends are promising, including the incorporation of artificial intelligence for more efficient analysis, the development of wearable and implantable biosensors, and the expansion of organs-on-chip for biomedical research. Microfluidics and biomedical devices are shaping the future of more efficient and personalized medicine.

Keywords: Microfluidics; Biomedical Devices; Biosensors; Clinical Applications.

RESUMEN

La convergencia de dispositivos biomédicos y microfluídica está revolucionando el diagnóstico y tratamiento en el sector de la salud, ofreciendo soluciones más rápidas, precisas y accesibles. La microfluídica, que manipula fluidos a escalas nanométricas y micrométricas, aprovecha principios como el flujo laminar y la difusión para permitir el desarrollo de sistemas miniaturizados. Los Laboratorios en Chip (Lab-on-a-Chip, LOC) son la materialización de esta simbiosis. Estos dispositivos integran múltiples funciones de laboratorio en una única plataforma, utilizando técnicas de fabricación como la fotolitografía y la impresión 3D. Su impacto es palpable en la detección rápida de patógenos, el diagnóstico de enfermedades crónicas y cáncer, el descubrimiento de fármacos y la medicina personalizada, facilitando pruebas en el punto de atención (POC) con volúmenes de muestra mínimos y costos reducidos. La integración de biosensores (ópticos,

electroquímicos, basados en ácidos nucleicos) en plataformas microfluídicas potencia la detección de biomarcadores con alta sensibilidad y especificidad. Esto se traduce en diagnósticos más tempranos y monitoreo continuo. Aunque estos avances prometen transformar la atención médica, persisten desafíos significativos. La escalabilidad de la producción, la reducción de costos, la armonización regulatoria y la necesidad de materiales biocompatibles son obstáculos cruciales. Sin embargo, las tendencias futuras son prometedoras, incluyendo la incorporación de inteligencia artificial para un análisis más eficiente, el desarrollo de biosensores vestibles e implantables, y la expansión de los órganos en chip para la investigación biomédica. La microfluídica y los dispositivos biomédicos están configurando el futuro de una medicina más eficiente y personalizada.

Palabras clave: Microfluídica; Dispositivos Biomédicos; Biosensores; Aplicaciones Clínicas.

INTRODUCTION

Microfluidics is a rapidly evolving field that amalgamates principles from physics, chemistry, biology, and engineering to precisely manipulate small volumes of fluids within microchannels.[1] This inherently interdisciplinary nature positions microfluidics as a key technology for driving innovation across a broad spectrum of biomedical applications. Its ability to integrate diverse perspectives and tools enables the development of solutions that traditional, fragmented approaches could not achieve.

This technology is crucial for modern healthcare as it has significantly transformed diagnostics and medical research, especially in drug discovery, gene therapies, and high-throughput screening.[2] Microfluidic devices are revolutionizing chemical and biological analysis by enabling precise control of fluids at a tiny scale, integrating assay and sample preparation operations on a single chip.[3] These systems offer advantages over conventional techniques, including minimal sample consumption, high efficiency, small device size, and integration of multiple functions.[4] The miniaturization and precise fluid control offered by microfluidics open new avenues for diagnosis and treatment, making it an essential pillar of today's advances in biotechnology and medicine.

To understand the magnitude of this technology, it is essential to establish clear definitions of key terms:

A microfluidic device is an instrument that uses tiny amounts of fluid in a microprocessor to perform laboratory tests.[5] These devices handle fluids within channels that typically range from 100 micrometers (µm) to 1 µm in diameter[6] and are designed to process fluid volumes as small as 10^{-9} to 10^{-18} liters.[3] A commonly used synonym for a microfluidic device, especially when it integrates multiple lab functions, is 'lab-on-a-chip' (LOC).[7,8]

Microfluidics, as a scientific field, is dedicated to studying and manipulating minute quantities of fluid through microchannels.[6,9,10] It encompasses the behavior, precise control, and manipulation of fluids geometrically confined to a small, usually sub-millimeter scale.[11]

A biomedical device, in a broader sense, is defined as any instrument, apparatus, machine, implant, in vitro reagent, or similar or related article, including its components or accessories, intended by the manufacturer to be used in humans for specific medical purposes, such as diagnosis, prevention, monitoring, treatment or mitigation of disease or injury. Crucially, its primary action is not achieved by pharmacological, immunological, or metabolic means, although they may assist it.[12] Examples of biomedical devices range from simple tongue depressors to complex pacemakers, imaging equipment, and computer software used in healthcare.[13] Regulatory bodies such as the FDA classify these devices according to risk, typically into Class I (low risk), Class II (moderate risk), and Class III (high risk).[14]

The interrelationship between these concepts is fundamental: microfluidics has emerged as a vital new field within Biomedical Engineering, specifically enabling the manipulation of fluids in channels at the scale of tens of micrometers.[15,16] This capability is essential for developing lab-on-a-chip diagnostics and drug screening platforms.[17] Consequently, microfluidic devices are integral to disease diagnosis, drug delivery, and disease monitoring applications, significantly impacting human health.[18] Their ability to precisely control fluids at the microscale is a central enabling factor for numerous biomedical applications.[19]

Brief History and Evolution of the Field

The origins of microfluidics lie in three main fields: microanalysis, biodefence, and microelectronics.[20] The technology emerged in the early 1980s, contributing to the development of inkjet printheads, DNA chips, and the fundamental concept of lab-on-a-chip technology.[7] The first lab-on-a-chip system was developed in the early 1980s.

The first documented lab-on-a-chip system designed for gas chromatography was developed in 1979 at Stanford University.[21] Significant research growth occurred in the late 1980s and early 1990s with the emergence of micropumps and integrated fluid analysis systems.[22] A significant boost for the field came in

the 1990s, driven by its applications in genomics, such as capillary electrophoresis and DNA microarrays, and by military development, particularly DARPA's interest in portable biochemical agent detection systems.[22] This development with multiple origins contributed to the robust and versatile nature of microfluidics, as it incorporated solutions to diverse engineering challenges before its potential in biomedicine was fully recognized.

Over the years, fluidics in medical devices has evolved from large, centralized systems to highly integrated and compact solutions, a transformation particularly evident in point-of-care (POC) diagnostics.[2] This evolution reflects a continuous drive towards miniaturization, precision, and accessibility in healthcare technology.

DEVELOPMENT

Fundamental principles of microfluidics

Microfluidics primarily involves the manipulation of fluids within channels that typically range from tens to hundreds of micrometers in dimension.[3] At this micro-scale, the behavior of fluids deviates significantly from what is observed at the macroscale; specifically, viscous and capillary forces become much more dominant, while the effects of gravity or inertia are significantly reduced.[9]

The nature of fluid flow, whether laminar or turbulent, is determined by the Reynolds number (Re), a dimensionless quantity. For microfluidic devices, small channel diameters (typically 10-100 µm) result in very low Reynolds numbers (generally below 2000), leading to a predominantly laminar flow regime. In laminar flow, fluid particles move in smooth, parallel lines with minimal turbulence, making the flow highly predictable. Consequently, the chaotic mixing common to macroscales does not occur; instead, mixing in microfluidic systems occurs primarily by diffusion between different fluid streams.[9] This predictable and controlled flow is essential for precise manipulation in chemical and biological processes.[19]

A significant feature of microchannels is their very high surface-to-volume ratio. This high ratio accelerates chemical reactions and significantly enhances heat and mass transfer within microfluidics.[4] In addition, the surface tension, resulting from cohesive forces between liquid molecules at the gas/liquid interface, is exceptionally high in microfluidics, a property that can be exploited for capillary pumping techniques. The dominance of these viscous and surface forces, leading to laminar flow and diffusion-based mixing, is the fundamental physical principle that enables the precise control and miniaturization inherent in microfluidics. Without these scale-dependent phenomena, the advantages of LOC systems and biosensors, such as low reagent consumption and fast reactions, would not be possible.[18]

Fluidic resistance is another critical aspect of microfluidics, defined by equations such as $Q = \Delta P/R$ (flow rate = pressure change/resistance), which is fundamental to optimizing fluid control systems and understanding the flow dynamics within channels.[18]

Fluid Control Mechanisms

Achieving precise control over fluid flow is paramount in microfluidic systems. The volumetric flow rate (Q) through a microchannel is governed by the Hagen-Poiseuille equation, which states that the flow rate increases with the fourth power of the channel radius. This relationship implies that while flow rates in microfluidic devices are inherently very low, they can be controlled with exceptional accuracy.[9]

The most common methods employed to generate and control the pressure differential, and consequently the fluid flow rate, within microfluidic systems include:

- Hydrostatic pressure: this is the simplest method, where the pressure differential is created by varying the height difference between the microfluidic channel and the fluid reservoirs.[9]
- Syringe pumps: These systems use a precisely controlled stepper motor to drive a mechanical system that pushes the plunger of a syringe at a constant, programmable speed. This results in a highly accurate and continuous flow of fluid. A key advantage of syringe pumps is their ability to control flow through microchannels independently of fluid resistance. Although they can cause pulsatile flow, there are methods to smooth out these fluctuations.[9]
- Pressure Generators: These devices apply controlled pneumatic (gas) pressure to a liquid reservoir connected to the microfluidic device, effectively driving fluid flow through the microchannels.[9]
- Peristaltic or roller pumps operate by a 'squeeze and release' action on a flexible tube to move the fluid, providing another mechanism for controlled flow.[9]

Some microfluidic devices can be driven by surface forces without external pumps, as seen in typical applications such as glucose meters and pregnancy tests.[23] The diversity of fluid control mechanisms, from simple hydrostatic pressure to advanced syringe pumps and pneumatic systems, responds to the varied requirements and complexity of microfluidic applications, balancing accuracy with cost and portability. The specific needs of each application, whether a simple diagnostic test or a high-throughput screening system, determine the choice of the most appropriate fluid control mechanism.

Lab-on-a-chip (LOC) systems

Lab-on-a-Chip (LOC) is a miniature device that integrates one or more laboratory functions on a single microchip, typicalmillimetersllimetres to fecentimetersntimetres.[23] These devices leverage microfluidics to replicate and miniaturize processes traditionally performed in a large-scale laboratory.[24,25]

The main advantages of LOC technology, which underline its transformative potential in biomedical applications, include:

- Miniaturisation and reduced consumption: LOCs can handle tiny fluid volumes, down to picolitres, significantly reducing reagent costs and sample consumption. This is particularly vital when dealing with expensive reagents or limited biological samples.[2]
- Automation and high-throughput screening: LOC devices enable advanced automation and high-throughput screening capabilities, allowing simultaneous analysis of multiple parameters. This accelerates processes in drug discovery and fundamental research.[2]
- Faster analysis and response times: Due to inherently short diffusion distances, rapid heating capabilities, and high surface-to-volume ratios within microchannels, LOCs offer significantly faster analysis and response times.[3] For example, microbial detection can be reduced from hours to mere minutes.[26]
- Portability and point-of-care (POC) testing: The compact and highly integrated nature of LOC devices makes them exceptionally portable, enabling on-site and point-of-care testing in various settings, including remote areas, field hospitals, and even home environments.[2]
- Improved Sensitivity and Specificity: by integrating advanced detection methods, such as optical, electrochemical, or magnetic detection, LOCs can achieve superior sensitivity and specificity in their analysis, thus improving diagnostic accuracy.[27]
- Contamination reduction: the fully enclosed design of many LOC systems inherently reduces the risk of sample contamination, ensuring greater data integrity.[28]
- Cost-effectiveness: the reduced reagent consumption and the reduced need for extensive traditional laboratory infrastructure contribute to a significant reduction in overall diagnostic and research costs.[3]

The advantages offered by LOC systems, such as miniaturization, speed, automation, portability, and cost-effectiveness, represent a paradigm shift from centralized laboratory analysis to decentralized and accessible diagnostics. This transformation has profound implications for global health equity, as it enables advanced testing in resource-constrained settings, bringing the laboratory to the patient rather than the other way around.

LOC device manufacturing

Microfluidic chip fabrication involves etching and processing on various substrates using advanced microprocessing technologies.[27] Historically, these devices were predominantly fabricated from silicon and/or glass, using techniques adapted from semiconductor fabrication.[28]

- Photolithography is a fundamental manufacturing technique borrowed from the semiconductor industry. It involves creating precise patterns on a substrate by spin-coating a light-sensitive photoresist, exposing it to UV light through a mask, developing the exposed photoresist, and then etching the substrate to transfer the desired pattern to the surface.[6]
- Soft lithography: A highly versatile and cost-effective technique, soft lithography uses elastomeric materials, polydimethylsiloxane (PDMS) being the most common. The process begins with the creation of a master mold (often fabricated by photolithography) and then replication of the desired microfluidic pattern on the PDMS substrate. PDMS is preferred for its optical transparency, elasticity, gas permeability, and biocompatibility. This method facilitates rapid prototyping and fabrication of complex microfluidic structures, making it accessible even in traditional laboratory settings.[18] However, PDMS has limitations, such as time-consuming processing, difficulty in achieving robust seals, swelling in the presence of many non-polar organic solvents, absorption of hydrophobic molecules, and incompatibility with high-throughput industrial processes such as thermoforming or injection molding.[29]
- 3D printing: this emerging manufacturing technique enables the creation of complex three-dimensional microfluidic structures with high precision and resolution directly from a digital model.[6] Common 3D printing technologies used include stereolithography (SLA), fused deposition modeling (FDM), and selective laser sintering (SLS). 3D printing offers significant advantages such as rapid prototyping, extensive customization, integration of multiple functionalities, and reduced manufacturing costs.[30] It is beneficial for testing specific designs efficiently before committing to mass production.[31]
- Micromachining/micro-milling/etching: these subtractive manufacturing processes start with a blank wafer or substrate and precisely etching or gouging channels and grooves.[32] Recent advances in micromachining technology have rapidly manufactured smaller, more complex structures at lower costs.

[33,34] Other related methods include microthermoforming, injection micro molding, and electro-spinning, each offering unique capabilities for creating microfluidic components.[6]

The evolution of manufacturing techniques, especially the shift towards 3D printing and the exploration of various polymers, indicates a strategic move to overcome the limitations of traditional semiconductor-based methods, such as high cost and reliance on clean rooms. This diversification is critical to achieving the scalability and cost-effectiveness required for widespread commercialization and point-of-care deployment.[35,36,37]

A wide range of materials is used in the manufacture of microfluidic devices, including traditional options such as glass and silicon and increasingly popular polymers such as PDMS, polystyrene (PS), polymethylmethacrylate (PMMA), polycarbonate (PC), cyclic olefin copolymer (COC), polypropylene (PP) and cellulose.[38,39] The selection of the appropriate material is paramount, as it fundamentally influences the device's performance, durability, chemical resistance, biocompatibility, and optical clarity.[40,41]

Table 1 compares the main techniques for the fabrication of microfluidic devices.

Table 1. Comparison of Microfluidic Device Fabrication Techniques

Manufacturing Technology	Key Principles / Typical Materials	Advantages	Limitations
Photolithography	Pattern creation with UV light in photoresist; substrate etching. Materials: Silicon, glass.	High resolution and accuracy; complex patterns.[38]	Costly; complex processing; clean room required.[17]
Soft Lithography	Replication of master moulds in elastomers (e.g. PDMS). Materials: PDMS.	Cost-effective; rapid prototyping; biocompatible; transparent.[18]	Slow processing; difficult sealing; swelling with organic solvents; absorption of hydrophobics; not compatible with industrial mass production[21].
3D printing	Layer-by-layer construction from digital model (SLA, FDM, SLS, PolyJet, inkjet, LOM). Materials: Polymers (e.g. PLA, light-curing resins).	Rapid prototyping; customisation; function integration; low cost; complex 3D structures[6].	Resolution and accuracy may vary; material properties; bonding/leakage problems in LOM[42].
Micromachining / Micro-milling / Engraving	Removal of material from a wafer to create channels. Materials: Silicon, polymers, metals.	Precision; suitable for wafer blanks; complex structures at low cost[6].	Subtractive process; may generate waste; machining speed in EDM[6].
Microinjection Moulding / Microthermoforming	Small-scale injection moulding/ thermoforming versions. Materials: Thermoplastics.	Cost-effective for mass production; high reproducibility[6].	High initial cost for moulds; less flexible for prototypes/small series[41].

Research and Clinical Applications

LOC systems can comprehensively analyze biochemical liquid samples, including metabolites, macromolecules, proteins, nucleic acids, cells, and viruses. They are instrumental in facilitating these samples' transport, sorting, mixing, and separation.[28]

Cell and Molecule Analysis

Microfluidics has been enthusiastically adopted in cell analysis because it integrates several modules, such as cell culture, sorting, and lysis, within a single miniaturized device. It is widely applied in cell cytometry, where precise flow control is essential, and the small size of the measurement system, comparable to the dimensions of a single cell, significantly improves sensitivity.[20]

Single-cell analysis has immense potential to study how individual cells influence disease progression and respond to treatment, overcoming the limitations of bulk analysis.[36] Microfluidics enables advanced single-cell analysis and high-throughput flow cytometry and provides critical insights in fields such as single-cell genomics. Recent innovations include the application of electrical impedance for efficient cell counting, recognition, phenotypic assays, and viability detection at the single-cell level.[42] The ability of microfluidics to precisely manipulate and analyze cells and molecules at their native scale, such as in single-cell analysis or rare cells such as circulating tumor cells, is a transformative advance in understanding disease mechanisms and developing highly sensitive diagnostics. This micro-scale precision directly translates into advances in liquid biopsy and personalized medicine.[43]

Cell separation using microfluidic devices offers an efficient method to isolate biological contaminants from body fluids and cell cultures, demonstrating its usefulness in purification processes.[19]

Detecting rare circulating tumor cells (CTCs) in peripheral blood is a non-invasive liquid biopsy technique of great importance for early cancer diagnosis, therapeutic efficacy monitoring, and personalized cancer treatment guidance.[44] Microfluidic devices, including innovative passive/active hybrid systems and inertial syringe tip centrifuges, have been developed specifically to achieve highly efficient and sensitive separation of

CTCs from complex blood samples.[45,46]

In DNA/nucleic acid analysis, microfluidics has played a key role in accelerating experiments, sequencing processes, and automation within large-scale projects such as the Human Genome Project.[23] Quantitative polymerase chain reaction (qPCR) systems integrated with microfluidics enable tenfold faster DNA amplification due to rapid thermal changes.[21] Also, nucleic acid-based biosensors integrate DNA amplification and hybridization steps on a single microfluidic platform, speeding up complex molecular analyses.[46] Microfluidic techniques also enable the use of microfluidic techniques to accelerate the sequencing and sequencing of DNA and DNA sequences.

Microfluidic techniques also allow the separation of protein molecules based on subtle differences in size, density, and compressibility, providing powerful tools for proteomics research.[47]

Disease and Organ-on-a-Chip (Organ-on-a-Chip) modelling

Organ-on-a-chip (OoC) systems are advanced microfluidic platforms designed to mimic biological functions and reproduce human tissue models in vitro to investigate the pathophysiology of diseases and novel therapeutic approaches.[1] These platforms integrate microfluidic channels with tissues replicating specific organ functions and microenvironments.[46] OoC systems are ideally suited to mimic biological functions and to reproduce human tissue models in vitro.

OoC systems are ideal for studying the effects of new drugs or toxicants on cells or organoids in a controlled and physiologically relevant manner. A significant advantage is their potential to replace traditional animal testing with in vitro analyses, which could substantially reduce the cost and time associated with drug discovery and production while addressing ethical concerns. In addition, OoC technology makes it possible to monitor the effects of drugs directly in a patient's cells, facilitating the evaluation and optimization of personalized treatments.[48]

This advance in manufacturing techniques, especially the creation of organ-on-a-chip models, allows for a more accurate mimicry of in vivo environments. This enhanced biomimicry capability is critical for drug discovery and personalized medicine, as it provides a more predictive platform for assessing the efficacy and toxicity of treatments, reducing reliance on less representative animal models.

Specific examples of organ models and their applications include:

- Neurobiology/brain-on-a-chip: microfluidic platforms are widely used to study neuronal communication, myelination processes, behavior, and axonal regeneration and to model neurodegenerative diseases such as Alzheimer's and Parkinson's. They allow the controlled replication of neuronal lesions and the study of microglial accumulation, which is relevant for chronic neuroinflammatory conditions.[18]
- Cancer modeling: microfluidic cell culture technology models complex cancer phenomena, including cell invasion, intravasation, extravasation, and the intricate tumor microenvironment.[46] This includes emulation of tumor-immune interactions.
- Lung-on-a-chip: these platforms are developed to assess drug toxicity under physiological conditions and to aid in drug screening.[46] They also simulate infection processes in lung organoids derived from chronic obstructive pulmonary disease (COPD) patients.[48]
- Liver-on-a-chip: used for in vitro studies of various liver disorders, particularly non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD), as well as for comprehensive toxicological evaluations of therapeutic agents.[46]
- Other notable examples of OoC systems include gut, bone, heart, and kidney models, each designed to replicate specific organ functions and allow for disease research and drug screening.[49]

Drug discovery and delivery

LOC devices are central to drug discovery, especially for their high-throughput screening capabilities. They can explore drug candidates, create personalized drug profiles for each patient, and assess drug efficacy and toxicity. This technology provides researchers with a window into drug interactions, allowing them to optimize formulations and speed up developing new treatments.[25]

Microfluidics offers a promising solution for drug delivery that is more efficient and targeted. It addresses the main disadvantage of conventional methods, such as oral administration, inhalation, or injection, where the drug's path from the inoculation site to the area of interest is often too long, rendering the treatment ineffective.[20]

Applications of microfluidics in drug delivery can be discussed at the cellular, tissue, and organism level:

- At the cellular level, microfluidics-based cell culture platforms can mimic in vivo conditions and generate diverse physicochemical environmental profiles, allowing the effects of drugs to be studied at the cellular level. They allow a precise and controlled flow of drugs into the culture chamber, making it possible to monitor cellular responses to high concentrations or other biochemical stimuli. Microfluidic gradient generators (MGGs) are key devices for testing drug responses at the cellular level, offering

higher resolution, real-time observation, adjustable drug concentration, and reduced cost compared to traditional methods.[20]

- At the tissue level, microfluidics is instrumental in the fabrication of 'smart particles' (micro/nanoparticles) that act as drug carriers for high-precision, localized delivery in diseased tissues. These particles can be bio capsules (to encapsulate transplanted tissue and prevent immune rejection), microparticles (to improve the efficacy of oral and intravenous administration), or nanoparticles (mainly used in cancer therapies to target malignant tissues).[20]
- At the organism level: while injection remains the most efficient method of whole-organism drug delivery, microneedles, miniaturized versions of conventional needles, are used to improve delivery efficiency and reduce pain. They can be solid, hollow, coated, or dissolvable, each with a specific mechanism of action and materials.[20] In addition, microfluidic systems can be used to improve delivery efficiency and reduce pain.

In addition, microfluidic systems manufacture implantable drug delivery devices, which can provide continuous or pulsed delivery to specific body areas, such as the brain or eye.[50,51]

Microfluidic biosensors

Biosensors are functional materials or devices capable of responding to biological activities and converting them into detectable signals. Their detection principle is based on the specific interaction between a compound or microorganism of interest and a biological recognition element.[52,53]

The key components of a biosensor include:

- Recognition element: the part of the biosensor that specifically interacts with the analyte of interest (e.g., enzymes, antibodies, nucleic acids, cells).[53]
- Transducer: after recognition, the transducer converts the changes resulting from the interaction of the recognition element into a measurable signal. They are classified as electrochemical, optical, and mechanical transducers depending on the type of signal they produce.[52]
- Signal processor: computational elements that amplify and process the signals the transducers produce, demonstrating them through numerical values and digital readouts.[54]

Integration of biosensors with microfluidic platforms

Integrating biosensors with microfluidic platforms has enabled the miniaturization, integration, and automation of disease diagnostic processes.[55] This combination offers an improved platform for analysis in various applications. By combining the concept of LOC with biosensors, easier and faster detection is achieved for multiple analyses.[27]

Due to their unique benefits, microfluidic systems are frequently used for biosensors to achieve miniaturization. On a single tiny chip, microfluidics allows the integration of sample pre-processing, signal identification, and signal transmission (including amplification and output). It also allows the use of multiple biosensors to achieve high detection performance. The integration of microfluidics and biosensors combines the benefits of both, characterized by accuracy, sensitivity, speed, and cost-effectiveness.[27]

Types of microfluidic biosensors and their detection mechanisms

Microfluidic biosensors are categorized into four main groups according to the elements they employ: enzyme-based, nano enzyme-based, antibody-based, and nucleic acid-based.[56]

Electrochemical biosensors

In electrochemical biosensors, changes in potential, current, conductivity, or impedance are used to detect the binding of the analyte on the sensing surface.[54] These biosensors are highly accurate, specific, and sensitive and have great potential for analyzing real samples. In addition, their design allows for a fast, low-cost, and straightforward format, making them compatible with handheld or wearable analyzers.[57]

Applications include multiplexed detection of multiple analytes from a single sample, improving diagnostic accuracy and therapy success.[58] For example, they have been demonstrated to measure antibiotics such as meropenem[58] and simultaneously detect biomarkers such as glucose and uric acid from a single drop of body fluid.[46] Electrochemical biosensors driven by enzymatic fuel cells are also an active area of research, offering energy self-support and timely online monitoring.[59]

Optical biosensors

Optical biosensors have attracted increasing interest due to their high sensitivity, specificity, and dynamic detection capability. They measure changes in optical parameters, such as wavelength and light intensity, when exposed to biological analytes. Optical responses can be based on various mechanisms, including fluorescence,

chemiluminescence, surface plasmon resonance (SPR), and surface-enhanced Raman scattering (SERS).[52]

Microfluidics plays an essential role in the fabrication of optical sensor materials, enabling the synthesis of nanomaterials with finely controlled size and physicochemical properties, which improves optical sensing performance.[52] Applications include the rapid and accurate measurement of critical biomarkers such as uric acid and glucose in handheld POC devices[60] and virus detection.[4]

Enzyme, nano-enzyme, and nucleic acid-based biosensors

- Enzyme-based biosensors use enzymes, mainly oxidoreductases, which are proteins that significantly accelerate reaction rates. They are highly selective, possess biocatalytic activity, and exhibit precise enzyme-substrate interactions, making them ideal for continuous monitoring and rapid and accurate analysis of various biomarkers. Integration with microfluidic platforms gives them automation, a small and stable detection area, and multiplexed functions. Applications include glucose monitoring (for diabetes management), lactate (for athletes and as a marker of tissue hypoxia), urea, and creatinine (for renal and liver health).[46]
- Nano-enzyme-based biosensors: these are nanomaterial-based artificial enzymes that mimic natural enzyme activity but offer advantages such as easy and inexpensive large-scale production, long storage times, and resistance to adverse conditions. They are effectively used for the colorimetric, electrochemical, and fluorescent measurement of glucose, hydrogen peroxide (H2O2), and point-of-care (POC) cancer diagnosis.[46]
- Nucleic acid-based biosensors involve amplifying target DNA fragments followed by DNA hybridization of the obtained sequences with complementary sequences immobilized on a single platform. They integrate amplification and base pairing with convenient detection methods. Types include polymerase chain reaction (PCR), CRISPR, and isothermal amplification (RCA, RPA, LAMP), all demonstrating remarkable efficiency and precision.[46]

Table 2 summarises the types and applications of microfluidic biosensors.

Table 2. Types and applications of microfluidic biosensors

Biosensor Type	Detection Mechanism	Key Bioelement	Typical Applications
Electrochemical	Changes in potential, current, conductivity, impedance.[54]	Enzymes, antibodies, nucleic acids, cells.[54]	Multiplexed detection of biomarkers (glucose, uric acid), drugs (meropenem), pathogens[46].
Optica	Changes in wavelength, light intensity; fluorescence, SPR, SERS, colorimetry.[52]	Functionalised nanoparticles, enzymes, aptamers.[34]	Detection of biomarkers (uric acid, glucose), viruses (Rotavirus, Ebola, Influenza).[4]
Enzyme-based	Biocatalytic enzymatic activity; hydrolysis, oxidation-reduction.[46]	Enzymes (e.g. glucose oxidase, lactate oxidase, urease).[46]	Monitoring of glucose, lactate, urea, creatinine; detection of pesticides.[46]
Nanoenzyme-based	Enzymatic mimicry of nanomaterials; colorimetric, electrochemical, fluorescence reactions.[46]	Nanoparticles (e.g. Fe3O4, Pt NPs).[46]	Glucose measurement,H2O2; POC diagnosis of cancer.[46]
Nucleic Acid Based	DNA/RNA amplification and hybridisation.[46]	DNA/RNA sequences, enzymes (Cas12), probes[46].	Pathogen detection (SARS-CoV-2, Zika), genetic analysis, liquid biopsy.[46]
Antibody-based	Antibody-antigen interaction.[46]	Monoclonal antibodies, Fab fragments.[46]	Detection of SARS-CoV-2 (IgG/IgM/antigen), foodborne pathogens.[46]

Applications of microfluidic biosensors in biomarker and pathogen diagnostics

Microfluidic biosensors are potent tools for biomarker and pathogen diagnostics, significantly impacting public health. In the field of liquid biopsy for cancer, they facilitate the isolation, enrichment, and detection of tumor markers such as circulating tumor cells (CTCs), circulating free DNA (ctDNA), microRNAs (miRNA), and exosomes.[4] This supports early diagnosis, accurate treatment, and prognostic assessment of various malignancies.[55]

Regarding the detection of pathogenic bacteria, microfluidic biosensors enable rapid, highly sensitive, and specific detection of various infectious agents, contributing to disease prevention and control and public health safety. This is especially relevant for foodborne pathogens such as Salmonella, Listeria, Cholera, and E. Coli, where combining functionalized nanoparticles with microfluidics improves sensitivity and speeds up the process.[34]

In addition, these biosensors are essential for general biomarker monitoring in various health conditions.

They allow continuous and accurate measurement of glucose, lactate, urea, and creatinine levels, which is vital for chronic disease management, physical performance monitoring, and organ function assessment. The ability to perform multiplexed analysis, i.e., to measure several biomarkers simultaneously in small amounts of biological fluids, represents a significant advance for diagnosing and monitoring complex diseases.[46]

Applications in clinical and point-of-care settings (POC)

Microfluidic devices have driven a transformation in the clinical setting, especially in developing point-of-care (POC) diagnostics performed close to the patient rather than in a centralized laboratory.[25] This evolution has been driven by the demand for faster diagnostics, reduced supply chain dependency, and the need for cost-effective instrumentation.[2]

Rapid diagnosis of infectious diseases

Microfluidic devices are revolutionizing infectious disease diagnostics by enabling rapid and accurate identification of pathogens. Unlike traditional methods that often require time-consuming cell culture, microfluidic-based molecular diagnostic techniques can reduce detection time to minutes to hours.[26]

Notable examples include:

- SARS-CoV-2: microfluidic-based detection strategies have been extensively developed for point-of-care diagnosis of COVID-19, categorised by detection mechanism: antigen detection, anti-SARS-CoV-2 antibody detection and nucleic acid detection.[34] Disposable chips with lyophilized probes and primers have been introduced for rapid detection in less than 30 minutes.[46]
- Dengue and Malaria: Technology bulletins highlight microfluidic technologies for detecting these diseases, underlining their importance in public health.[3]
- Hepatitis C virus: an inexpensive, disposable, self-powered microfluidic chip has been developed that performs the entire virus detection process in approximately 45 minutes, requiring only a small amount of sample and few reagents.[35]
- Foodborne pathogens: At a lower cost, microfluidic devices can detect pathogens such as Salmonella, Staphylococcus, or E. coli in food samples, as well as toxins and heavy metals.[32]

Biomarker monitoring

Integrating microfluidic systems with machine learning has advanced real-time monitoring of biochemical biomarkers, contributing to personalized healthcare and fitness tracking.[61] This includes the development of skin-interconnected microfluidic patches that, equipped with machine learning-based image processing, analyze sweat biomarkers in real time, overcoming challenges such as inconsistent lighting and motion artifacts.[62]

Specific examples of biomarkers monitored include:

- Glucose and lactate are essential for diabetes management and physical performance monitoring. Off-pump microfluidic enzyme pump systems have been developed for glucose measurement from a single drop of non-invasive biofluids and systems for continuously monitoring lactate in sweat.[63]
- Circulating tumor cells (CTCs): detection of CTCs in peripheral blood is a promising indicator for early cancer diagnosis and monitoring.[4]
- Cardiovascular biomarkers: portable, rapid-response microfluidic platforms detect cardiovascular disease-related biomarkers in minutes from small clinical samples.[64]

Personalized medicine and targeted therapies

Microfluidics is transforming medicine by enabling the creation of treatments tailored to the individual characteristics of each patient, known as personalized medicine.8 Organ-on-a-chip systems are central to this, as they allow the effects of drugs to be monitored directly in a patient's cells deposited on the chip, facilitating the assessment and optimization of personalized treatments. This ability to tailor treatments based on genetic data and individual cellular responses provides a more precise and practical approach to healthcare.[65] In addition, microfluidics can also be used to improve the efficiency and effectiveness of treatments.

In addition, microfluidics contributes to developing theranostics, which combine therapeutic and diagnostic capabilities in a single entity. Microfluidic systems are used to create theranostic nanoparticles that can monitor drug delivery and release, determine the cancer stage, and mediate drug delivery at appropriate doses.[32]

Low-cost, portable devices for the home and remote areas

Portability and low cost are inherent advantages of microfluidic devices, making them ideal for point-of-care (POC) applications and resource-limited settings. The World Health Organisation (WHO) has established criteria for POC diagnostic devices, summarised by the acronym ASSURED: Affordable, Sensitive, Easy to use, Fast and robust, Equipment-free, and Deliverable to end-users.[32]

Microfluidics that meet these criteria include pregnancy tests, COVID-19 tests, and blood glucose monitoring

strips. These disposable lateral flow systems provide on-site results with a rapid turnaround time, democratizing access to healthcare services by eliminating the need to send results to a centralized laboratory.[25]

Microfluidics offers great utility in low- and middle-income countries (LMICs), where healthcare infrastructure is less developed, as it enables access to appropriate diagnostics and treatment without using rare and expensive drugs.[21] Integrating microfluidic devices with smartphones is a promising trend for miniaturizing screening and analysis schemes.[27] Brightfield or fluorescence microscopy adapters, often 3D printed for cost-effectiveness, can be attached to smartphones with good CMOS cameras, using LEDs, the phone's torch, or ambient light for illumination. Smartphones can also be integrated with amperometric biosensors for electrochemical sensing, serving as analyzers and processors. This integration leverages the ubiquity of smartphones to make POC diagnostics more accessible and affordable globally.[34]

CONCLUSIONS

Microfluidics has emerged as a transformative technology in the biomedical field, driving significant innovations in developing laboratory-on-a-chip (LOC) systems, biosensors, and diagnostic devices. This discipline has revolutionized research and clinical practice by enabling the precise manipulation of fluids at the microscale.

Despite microfluidics' remarkable advances and immense potential in the biomedical field, significant challenges need to be addressed for its widespread adoption and commercialization. The manufacturing process of microfluidic devices is inherently complex and requires intensive labor, specialized equipment, and highly skilled personnel.

The choice of materials is a critical factor affecting the performance and durability of microfluidic chips. It is an ongoing challenge to find materials that can be economically processed both on a small scale for research and on a large scale for commercial production.

The future of biomedical devices and microfluidics looks promising, with several emerging trends that will further boost their impact on healthcare. Microfluidic devices have the potential to democratize access to healthcare, especially in low- and middle-income countries, by offering affordable, portable, and easy-to-use diagnostics that do not require complex laboratory infrastructure. This improved accessibility can lead to earlier detection and treatment of diseases, improving health outcomes globally.

In addition, microfluidics is a cornerstone of precision medicine. Enabling detailed analysis of individual cellular responses to treatments and creating personalized disease models facilitates the development of more targeted and effective therapies. The trend towards sustainability in manufacturing, focusing on biodegradable materials and greener production processes, will also contribute to a positive environmental impact in the healthcare sector.

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