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A Comprehensive Review on the Miniaturized Analytical Techniques for Sustainable Pharmaceutical Testing

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Abstract

Miniaturized analytical techniques are revolutionizing pharmaceutical testing by offering sustainable and efficient alternatives to traditional methods. These techniques are designed to reduce sample and reagent consumption, minimize waste generation, and accelerate analysis, aligning perfectly with the principles of green analytical chemistry. This comprehensive review aims to thoroughly explore the landscape of miniaturized analytical techniques, specifically highlighting their profound impact on fostering sustainable practices within the pharmaceutical sector. The review systematically covers miniaturized sample preparation strategies, which are crucial for reducing the environmental footprint of analytical processes. It examines advanced microextraction techniques, including solid-phase microextraction, liquid-phase microextraction, and stir-bar sorptive extraction, detailing how these methods significantly decrease solvent usage, improve sample throughput, and enhance sensitivity by concentrating analytes. Furthermore, the discussion extends to miniaturized separation technologies, such as capillary electrophoresis, microchip electrophoresis, and nano-liquid chromatography. These techniques are lauded for their exceptional separation efficiency, minimal sample requirements, and reduced operational costs, making them ideal for complex pharmaceutical matrices. Finally, the article delves into the integration of these miniaturized approaches with modern detection systems and automation, discussing how they contribute to the development of robust, high-throughput, and environmentally friendly analytical workflows. It addresses the challenges and future prospects of adopting these technologies on a wider scale, including regulatory considerations, validation issues, and the continuous need for innovative solutions to further enhance sustainability in pharmaceutical testing. The overall goal is to provide a holistic understanding of how miniaturization is not just a trend but a critical evolution towards more sustainable, efficient, and cost-effective pharmaceutical analysis.

Keywords: Miniaturized analytical techniques, sustainable pharmaceutical testing, green analytical chemistry, microextraction, nano-liquid chromatography

INTRODUCTION

Background

Sustainability in analytical sciences involves a paradigm shift to align with sustainability science, moving beyond just reducing waste to encompass economic stability and social well-being. This concept recognizes the crucial role analytical chemistry plays in environmental monitoring, despite its own practices contributing to environmental degradation. The goal is to drive sustainability forward by reducing solvent use, adopting miniaturized systems, and employing remote diagnostics to minimize travel for service engineers. Sustainable practices in the use of analytical instruments are considered crucial for reducing energy consumption, minimizing waste, and optimizing resource use [1]. In analytical chemistry, "sustainability" and "circularity" are frequently used interchangeably. Circularity may

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not take into account all three aspects of sustainability (economic, social, and environmental), even if its main goals are waste reduction and extending the life of materials. The social component is less prominent in the circular analytical chemistry framework, for instance, but economic and environmental factors are heavily integrated. Nonetheless, innovation acts as a link between sustainability and circularity, while sustainability propels advancements toward more circular practices. Additionally, embracing circular ideas might serve as a springboard for accomplishing more general sustainability objectives [2].

Green Analytical Chemistry (GAC) is defined as the optimization of analytical processes to ensure they are safe, non-toxic, environmentally friendly, and efficient in their use of materials, energy, and waste generation. GAC encourages minimizing the use of toxic chemicals and reagents, utilizing energy-efficient equipment, and generating minimal waste [3]. The field of GAC is guided by 12 principles that prioritize sustainability, providing a framework for developing effective and environmentally friendly methodologies. Throughout the preparation, pre-treatment, and determination phases of the analytical process, these guidelines seek to minimize or completely eradicate hazardous and toxic solvents, reagents, and procedures. Analytical techniques have historically frequently depended on hazardous reagents and solvents, producing large amounts of waste and endangering the environment as well as analysts. GAC tackles these problems by creating techniques that are more sustainable and safer by nature. With example, one of the core tenets of GAC is substituting safer chemicals and solvents with dangerous ones. Therefore, green analytical chemistry concentrates on process optimization to be safe, non-toxic, and effective, whereas sustainability in analytical sciences includes economic, societal, and environmental pillars. These concepts aim to minimize environmental impact, reduce waste, and improve safety in all chemical processes [4].

The need for miniaturization in analytical techniques stems from a confluence of factors, including the drive for enhanced efficiency, reduced costs, and improved analytical performance. This long-term trend in clinical diagnostics and analytical chemistry has gained renewed impetus due to various perceived benefits and practical requirements. Smaller systems require significantly less reagents and solvents, leading to substantial cost savings and reduced chemical waste. For instance, in High-Throughput Screening (HTS) in the pharmaceutical industry, assay miniaturization reduces the consumption of expensive biochemical reagents, leading to dramatic cost savings [5]. In HPLC, miniaturization reduces solvent usage, instrumentation, and column size. Operating at a smaller scale often leads to faster reaction times and quicker analytical results due to enhanced control over molecular interactions at the microscale level. This is particularly beneficial in drug discovery, where faster assay development and shorter screening times accelerate the R&D cycle [6]. Beyond reagents, miniaturization helps reduce the overall instrumental space and manufacturing costs, making analytical tools more accessible and affordable. This includes the development of portable instruments that are small and cheap, yet highly effective. By reducing sample volumes, miniaturized assays can expand the scale of testing, facilitating rapid analysis of numerous samples, which is crucial in areas like cell-based microplate assays and drug discovery. Miniaturized systems often achieve higher sensitivity due to reduced chromatographic dilution and improved ionization efficiency, especially in techniques like miniaturized liquid chromatography coupled with mass spectrometry (LC-MS). This allows for the analysis of smaller sample volumes and detection of analytes at lower concentrations. Techniques such as capillary electromigration and nano-LC offer high chromatographic resolution and efficiency, which are significant advantages over conventional methods in separation science [7].

Many analytical applications, particularly in fields like clinical diagnostics and drug discovery, deal with limited sample volumes. Miniaturization allows for the analysis of sub-microliter volumes, making it possible to work with precious or scarce samples, such as those from small rodent studies or neurological samples. Analytical measurements are more reliable and reproducible when microfluidics and molecular interactions are precisely controlled at the microscale. Additionally, miniaturization meets a number of strategic and pragmatic demands across a range of businesses. Instead of requiring samples to be transferred to a central laboratory, on-site or in-field analysis is made possible by more

portable, smaller, and more portable analytical equipment. This is especially helpful for medical diagnostics, process control, and environmental monitoring [8]. As a direct outcome of miniaturization, lab-on-a-chip (LOC) technologies combine several analytical processes, from sample preparation to detection, onto a single chip. Improved analytical performance, less manual intervention, and automated analysis are the results of this integration. The pharmaceutical industry requires microscale, massively parallel drug discovery assays to accelerate research and development [9]. Miniaturization in HTS is considered essential for handling the increasing number of compounds and targets, accelerating the R&D cycle, and reducing costs. Miniaturization aligns with green chemistry principles by reducing the consumption of reagents and solvents and minimizing waste generation, contributing to more sustainable analytical practices. New technologies like micromachining and molecular self-assembly provide the means for further size reduction, pushing the boundaries of analytical capabilities to micro to nanometer dimensions. This includes the miniaturization of optical remote sensors, antennas, and mass spectrometry instruments [10].

COMPARISON BETWEEN CONVENTIONAL AND MINIATURIZED ANALYTICAL SYSTEMS

Miniaturized analytical systems offer compelling advantages over conventional systems due to advancements in various technologies. These benefits span from reduced operational costs and enhanced analytical performance to improved portability and sustainability. The differences between conventional and miniaturized analytical systems have been summarised in Table 1.

Table 1. Comparison between conventional and miniaturized analytical systems [5–14].

Parameter	Conventional Analytical Techniques	Miniaturized Analytical Techniques	Remarks / Sustainability Impact
Sample Volume	Typically 1–10 mL	Often <10–100 µL (sometimes <1 µL)	Significant reduction in sample requirement, suitable for limited or costly samples
Solvent Consumption	High (tens to hundreds of mL per run)	Very low (few µL to mL per run)	Major reduction in solvent use → greener and cost-effective
Reagent Usage	Large quantities required	Minimal reagent quantities	Less chemical waste and safer handling
Analysis Time	Moderate to long (10–60 min/run)	Short (seconds to few minutes/run)	Faster throughput and higher productivity
Instrument Size	Bulky, bench-top systems	Compact, portable, or chip-based devices	Enhanced portability and on-site applicability
Energy Consumption	Relatively high	Lower due to smaller systems	Reduced carbon footprint
Sensitivity / Detection Limits	High but dependent on method	Comparable or sometimes higher due to micro-scale precision	Miniaturization can enhance mass transfer and improve detection
Precision / Reproducibility	Well-established, high reproducibility	Improving; may vary with design and fabrication	Requires optimization and standardization
Automation / Integration	Limited, often manual operations	Highly automatable and integrable with sensors	Enables real-time and in-line analysis (PAT-compatible)
Waste Generation	Significant chemical waste	Minimal waste generation	Contributes to green analytical chemistry goals
Cost per Analysis	Higher (due to solvents, reagents, waste disposal)	Lower operational cost	Economical in long-term use
Regulatory Acceptance	Widely accepted	Emerging and gaining acceptance	Increasing validation studies support adoption

Size and Portability

- *Conventional Analytical Systems:* These systems are typically larger and often require dedicated laboratory space for operation. Their size limits their mobility, making them unsuitable for on-site or in-field analysis.

- *Miniaturized Analytical Systems:* Miniaturization enables the production of novel systems that are substantially reduced in size, ranging from micro- to nanometer dimensions. This reduction in size significantly enhances portability, allowing analyses to be performed outside traditional laboratories, such as in critical care units, disaster relief efforts, or for forensics testing. Examples include devices that can fit into the palm of a hand or be integrated into portable mass spectrometry systems [11].

Reagent and Solvent Usage
- *Conventional Analytical Systems:* These systems generally consume larger volumes of reagents and solvents, which can be costly and generate more chemical waste.
- *Miniaturized Analytical Systems:* One of the primary advantages of miniaturization is the reduced consumption of reagents and solvents, leading to lower operating costs and less waste generation. For instance, miniaturized columns in liquid chromatography use significantly less solvent [12].

Cost
- *Conventional Analytical Systems:* Higher consumption of reagents and larger instrumentation contribute to higher operational and manufacturing costs.
- *Miniaturized Analytical Systems:* Miniaturization helps reduce instrumental space and manufacturing costs. The decreased consumption of expensive reagents also contributes to significant cost savings [11].

Analysis Speed
- *Conventional Analytical Systems:* Analysis times can be longer due to the larger scale of operations.
- *Miniaturized Analytical Systems:* Operating at a smaller scale often leads to faster reaction times and quicker analytical results. This is particularly evident in micro total analysis systems (μTAS), which offer higher speed and better separation performance [8].

Sample Volume
- *Conventional Analytical Systems:* Typically require larger sample volumes for analysis.
- *Miniaturized Analytical Systems:* These systems are designed to handle extremely small sample volumes, down to sub-microliter or even pico-litre levels. This is crucial for applications where samples are limited, such as in biological or medical investigations [6].

Sensitivity
- *Conventional Analytical Systems:* Possess standard levels of sensitivity.
- *Miniaturized Analytical Systems:* Miniaturization can improve the sensitivity of analytical methods, especially when combined with appropriate sample preparation techniques. For example, miniaturized liquid chromatography (LC) can offer higher overall sensitivity than conventional LC. Capillary-based separation systems also provide better mass limits of detection [3].

Integration and Automation
- *Conventional Analytical Systems:* Often consist of separate, modular components, requiring manual interfacing between different steps of the analytical process.
- *Miniaturized Analytical Systems:* μTAS integrates multiple steps of a chemical analysis, such as sample input, reaction chambers, separation, and detection, onto a single chip. This integration enables automated analyses and reduces the need for human intervention [6].

Complexity of Procedures
- *Conventional Analytical Systems:* Procedures for analysis, particularly in complex techniques like mass spectrometry, can be intricate and time-consuming.
- *Miniaturized Analytical Systems:* Efforts in miniaturization include developing systems with simplified operational procedures, making them accessible to novice users outside of traditional analytical laboratories [8].

Environmental Impact

- *Conventional Analytical Systems:* Higher consumption of chemicals and larger waste generation lead to a greater environmental footprint.
- *Miniaturized Analytical Systems:* Reduced consumption of reagents and solvents and less waste generation make miniaturized systems more environmentally appealing. The establishment of greener laboratories is a direct result of introducing miniaturized systems [7].

TYPES OF MINIATURIZED ANALYTICAL TECHNIQUES

Micro-Scale Chromatography

Miniaturized HPLC (µHPLC, nano-HPLC, capillary LC)

Miniaturized High-Performance Liquid Chromatography (Miniaturized HPLC), including micro-HPLC (µHPLC), nano-HPLC, and capillary LC, plays a significant role in ensuring sustainability within analytical chemistry, particularly in pharmaceutical testing. This is primarily due to its alignment with green chemistry principles by reducing resource consumption, waste generation, and environmental impact. Miniaturized HPLC systems operate with significantly lower flow rates compared to conventional HPLC, which drastically reduces the consumption of mobile phase solvents. For example, scaling down the column inner diameter from 2.1 mm to 0.300 mm can lead to a 98% reduction in resource consumption. This directly translates into less hazardous waste generation, a core principle of green analytical chemistry. The reduction in solvent usage not only benefits the environment but also leads to considerable cost savings, making the analytical process more economically sustainable [15]. Studies have shown that even minor modifications to conventional equipment, such as using micro-detector cells, can enable the routine use of smaller-bore columns, resulting in a considerable reduction in the use and costs of organic solvents. Miniaturized columns lead to a reduction in chromatographic dilution and an increase in sensitivity. This allows for the analysis of smaller sample amounts and the detection of analytes at lower concentrations, which is particularly valuable in fields like proteomics, metabolomics, and lipidomics where sample volumes can be limited. This improved sensitivity means that less sample material is needed, further contributing to resource conservation [16]. While increased gradient length in some low-flow chromatography applications can reduce sample throughput, micro-flow offers a great intermediate option when sample throughput, sensitivity, and robustness are desired. The ability to analyze samples quickly and efficiently reduces overall energy consumption per sample. Advances in instrument miniaturization have enabled the development of portable LC instrumentation. This capability allows for in-situ monitoring, reducing the need for sample transportation to a centralized lab, thereby saving energy and resources associated with logistics [17]. The miniaturization of HPLC, particularly through capillary LC (c-LC) and nano-LC (n-LC), provides inherently green methodologies. These techniques align with the broader goals of green analytical chemistry by minimizing the environmental impact of analytical procedures. Miniaturized systems often require less handling of hazardous materials due to smaller sample and reagent volumes, which improves laboratory safety. Miniaturized sample preparation techniques, such as on-line and off-line methods like in-tube solid-phase microextraction (IT-SPME), minimize sample treatment and allow direct sample injection. These methods offer high selectivity, efficient sample clean-up, and significant enrichment factors, further contributing to green and sustainable practices [18].

Micro-GC and Portable GC Systems

Micro-Gas Chromatography (Micro-GC) and portable Gas Chromatography (portable GC) systems play a crucial role in promoting sustainability by enabling efficient, on-site environmental monitoring, reducing resource consumption, and enhancing the overall greenness of analytical chemistry. These systems offer significant advancements over traditional laboratory-based GC methods, contributing to sustainability in several ways. Micro-GC systems, which have seen significant development over the past four decades, contribute to sustainability through their miniaturized components and reduced operational demands. Micro-GC systems require significantly less power and carrier gas compared to conventional GCs. This reduction in consumption is crucial for minimizing the environmental footprint of analytical operations [19]. The smaller size and advanced technology of Micro-GCs lead to less material waste, contributing to a more sustainable laboratory environment. Some Micro-GC systems,

like the Agilent 990, are manufactured with a high percentage of recycled content in their components (nearly 90% in steel, resulting in over 20% sustainable content by weight) and packaging (over 60% sustainable content in cardboard boxing). This reduces the demand for virgin materials and supports circular economy principles. The use of electronic pneumatics control (EPC) modules in Micro-GC systems allows for the use of alternative carrier gases instead of helium, which is a non-renewable resource, further enhancing sustainability. During their use phase, Agilent 990 Micro GC Systems do not consume water, which is a significant environmental benefit [16]. Faster detection and reaction to environmental problems are made possible by the potential of micro-GC systems for the on-site, quick analysis of complicated chemical mixtures. For pollution management and environmental risk assessment, this quick analysis capability is essential. Businesses can optimize production processes and lower emissions by incorporating Micro-GC into environmental monitoring systems, which will help them satisfy sustainability objectives and environmental requirements. The ability of micro-GC Fusion systems to measure and report gas component data in mole percentage is essential for figuring out heating value and comprehending fuel composition, which helps with energy efficiency. When used with micro-GC columns, micro pre-concentrators can efficiently concentrate environmental trace samples, significantly increase detector response, and enable more precise pollutant analysis. MEMS-enabled Micro-GC/PID systems are being developed for high-sensitivity profiling of VOCs, even with sub-ppb detection limits using ambient air as the carrier gas. This technology is crucial for real-time air quality assessment and odour dispersion modelling, particularly for anthropogenic emissions [20].

Portable GC and field-portable GC-MS systems have revolutionized environmental sample analysis by bringing laboratory capabilities to the field. Portable GC-MS systems play a major role in environmental and forensic applications that require rapid identification of substances. Their ability to provide immediate results on-site minimizes the need to transport samples, thereby reducing logistical environmental impacts. These instruments have proven usable in challenging conditions, such as jungles and chemical demilitarization zones, highlighting their robustness for critical environmental monitoring [21]. Portable GC-MS is used for the rapid, qualitative analysis of organic pollutants and for detecting VOCs/SVOCs in various samples, including indoor air. Portable GC systems, such as the XG-100, can use ambient air as the carrier gas, eliminating the need for pressurized gas cylinders (N_2, He, H_2) and thereby reducing energy consumption and associated costs [22]. Some portable GC-MS columns allow for faster temperature changes, leading to roughly 1% of the energy consumption of larger systems. Increased portability in analytical chemistry promotes a more democratic and sustainable approach, making advanced analytical capabilities accessible for broader environmental monitoring efforts [23].

Chip-Based LC and Hybrid Systems

Chip-based Liquid Chromatography (LC) and hybrid analytical systems offer significant contributions to sustainability by reducing resource consumption, minimizing environmental impact, and providing efficient analytical solutions across various fields. Often called lab-on-a-chip devices, chip-based LC systems are miniature analytical instruments that combine several laboratory operations onto a single chip [24]. They benefit from sustainability in a number of important ways. The amounts of reagents and solvents needed for analysis are greatly decreased using chip-based LC systems. This reduces waste production, which is essential to environmental preservation and green chemistry concepts. Comparing these systems to traditional LC instruments, their smaller size frequently results in the use of less material during construction. While this reduces initial material impact, the disposal of single-use polymeric microfluidic devices can pose environmental challenges if not managed sustainably. The smaller scale of operation can lead to reduced energy consumption during analysis, contributing to lower operational carbon footprints. Sustainable practices in the production and disposal of these devices are crucial to avoid additional CO_2 release, especially for single-use devices that might require incineration for infection control. Chip-based LC enables high-speed enantio-separations, which can make analytical processes more efficient [25]. Faster analysis means quicker results and potentially less energy spent per sample. These systems offer enhanced sensitivity, allowing for accurate analysis with smaller sample volumes. This is particularly beneficial in fields like proteomics, where sample

availability can be limited. Chip-based nano-LC-MS technology has proven to be a highly stable and reliable platform for profiling N-glycans, which is crucial for biomarker discovery and the diagnosis and treatment of diseases. Its excellent repeatability, with average intra-day CVs of 2.1% ± 1.7% and inter-day CVs of 3.9% ± 1.4%, ensures consistent data for large biomarker studies [26]. The portability of chip-based systems can enable field-deployable analysis for environmental monitoring and point-of-care diagnostics, reducing the need for sample transport and allowing for rapid, on-site decision-making. Chip-based LC systems are frequently coupled with MS, benefiting from lower flow rates that are more compatible with electrospray ionization (ESI) and enabling the identification of potential glycoprotein biomarkers in complex protein mixtures [27].

Hybrid analytical systems combine different analytical techniques or integrate various components (e.g., renewable energy sources) to achieve synergistic benefits, often with a focus on sustainability. While the term "hybrid analytical systems" can refer to various combinations, a prominent area of sustainability is in hybrid renewable energy systems (HRES) [28]. Hybrid systems, particularly those integrating renewable energy sources with conventional power generation or other technologies, significantly reduce greenhouse gas (GHG) emissions and improve air quality. For example, a hybrid system can reduce CO_2 emissions from 21.8 to 10 tons, and particulate matter (PM) from 4.1 to 1.9 kg. By combining multiple renewable sources (like solar and wind) and often incorporating energy storage solutions, HRES increases the penetration of renewable energy into the grid, decreasing reliance on fossil fuels [29]. Hybrid solar PV-battery systems can reduce grid dependency, helping to balance electricity supply and demand. Hybrid systems can lead to more optimal use of resources, such as water in hydropower-floating solar photovoltaic systems, by reducing curtailment and improving operational efficiency. Hybrid electric vehicles offer environmental benefits by reducing CO_2 emissions, even outperforming battery electric vehicles in some contexts due to scarce battery capacity. By substituting electronic actuation systems for hydraulic and pneumatic ones, hybrid aircraft actuation systems also help the environment by being more reliable, lighter, and requiring less maintenance. Economic factors are taken into account when optimizing hybrid systems to make sure they are sustainable and affordable [27]. Particularly in isolated areas, incorporating renewable energy into the production of electricity promotes sustainable development by lowering costs, increasing energy security, and improving sustainability. HRES are the best options for reducing the use of fossil fuels, meeting the growing demand for power in remote locations, and resolving related economic and environmental issues. In some cases, hybrid renewable energy systems can improve the quality of life in rural communities by providing reliable electricity, though effective implementation requires strong institutional frameworks and community participation [30].

Miniaturized Electrophoretic Techniques

Miniaturized electrophoretic techniques like capillary electrophoresis (CE) and microchip electrophoresis (MCE) play an increasingly significant role in environmental sustainability by offering efficient, low-cost analytical solutions and reducing chemical consumption. Clinical diagnostics, food analysis, pharmaceutical research, and environmental monitoring are just a few of the many uses for these technologies. Because of its ease of use, effectiveness, and affordability, CE is a useful instrument for environmental monitoring [31]. It helps with better pollution control by detecting organic and inorganic ions as well as heavy metals in the environment. Additionally, CE is used to detect a variety of environmental contaminants at trace quantities, such as bacteria, viruses, explosives, pesticides, and polycyclic aromatic hydrocarbons. It is especially well-suited for monitoring environmental samples due to its capacity to assess small amounts and weak concentrations of contaminants [32]. Because of its low sample volume requirements, quick analysis times, and decreased solvent and residue formation, CE stands out as a green analytical approach. The miniaturization inherent in CE technology significantly reduces the amount of chemicals needed for analysis and decreases overall sample processing times, making it a sustainable choice in liquid phase separation science [33].

MCE, also known as nano-capillary electrophoresis, represents a miniaturized form of CE that further enhances sustainable practices. MCE devices are designed to analyze extremely small sample volumes,

improving the speed and throughput of chemical and biochemical analyses while reducing costs. This miniaturization allows for rapid separations, often within seconds, and offers high resolution and significant peak capacity [34]. These devices also offer features like portability, integration, and high-throughput capabilities. Environmental agencies are using MCE more and more to find pollutants in samples of soil, water, and air. It is essential for tracking trace contaminants that could otherwise go unnoticed because it can detect a variety of environmental pollutants at nanogram to picogram levels [35]. The method is regarded as a unique approach for environmental sample analysis because of its adaptability, speed, sensitivity, and low operating costs. Because microchip electrophoresis lessens the environmental impact of analytical processes, it is in line with sustainable development goals [36]. Its capacity to function with small amounts of reagents and samples helps to reduce energy use and chemical waste. Additionally, developments in MCE concentrate on combining several operations into small, single units, which enables the analysis of numerous samples in parallel and further minimizes resource use. This technology also shows promise in areas such as DNA analysis for modern biotechnology, particularly in genomic, proteomic, and genetically modified organism research [37].

Miniaturized Spectroscopic Methods

Micro-Attenuated Total Reflectance Fourier Transform Infrared (Micro-ATR-FTIR), portable Raman, and handheld Near-Infrared (NIR) spectroscopies are valuable tools contributing to sustainability and green chemistry by enabling rapid, non-destructive, and in-situ analysis with minimal sample preparation and reduced chemical waste [38].

Micro-ATR-FTIR is a powerful analytical technique that allows for the non-destructive investigation of molecular composition by measuring infrared light absorption at a sample-crystal interface. Micro-ATR-FTIR often requires minimal or no sample preparation, which significantly reduces the use of solvents and reagents, aligning with green chemistry principles. This is especially helpful when working with polymer materials because the method can manage different sample sizes and shapes without the need for additional conditions. Real-time, in-situ monitoring of a variety of processes, including polymer degradation reactions, is possible using this technology. Additionally, it makes it easier to research dynamic aqueous systems, microfluidics, dissolution, diffusion, and dynamic processes in living cells [39]. Because it offers comprehensive details on chemical composition, particle morphology, and pollution pathways, micro-ATR-FTIR is essential in the study of microplastic pollution. In intricate environmental matrices, it is very useful for locating and identifying tiny microplastics and can even reveal details about their size. Micro-ATR-FTIR, particularly in ATR mode, is used in environmental microbiology to directly and non-destructively examine the chemical makeup of microbial biofilms, even in aqueous media. This allows for monitoring biofilm development, maturation, and responses to environmental cues, offering insights into their impact on broader ecological systems. The technique contributes to the preservation and analysis of cultural heritage objects by providing high-resolution chemical maps of painted stratigraphies and other artistic materials [40].

Portable Raman spectrometers offer a rapid, non-destructive, and often in-situ method for material analysis across various fields, contributing significantly to sustainability and green chemistry efforts. Portable Raman spectrometers are utilized by environmental scientists to monitor pollutants and analyze environmental samples in remote locations. This capability is enhanced by the ability to detect organic or inorganic, airborne or waterborne, and embedded or adsorbed analytes within environmental systems [41]. They can also be used for in-situ soil analysis, which is essential for assessing and tracking soil health as a sustainable habitat, and for quick study of water pollution. By guaranteeing quality, portable Raman devices assist prevent food fraud and improve traceability in supply chains, including those involving palm oil. They can also be used to identify pesticides in fresh produce and track the quality of food as it is being transported [21]. In order to lower exposure hazards, portable Raman is essential for detecting dangerous substances, illegal drugs, explosives, and chemical weapons, frequently through clear packaging. Features for quick detection and analysis in the field are part of the development of these devices. Raman spectroscopy's portability and non-destructive nature minimize sample change

and waste, which is consistent with the concepts of green analytical chemistry [42]. Advances include integration with microfluidic chips to improve detection sensitivity and reproducibility for hazardous materials analysis. Portable Raman is advancing sustainable farming practices by offering quick results and economic benefits. It can be used for early detection of biotic stress in plants and real-time monitoring of various reactions in aqueous media [43].

Handheld NIR spectrometers are recognized as powerful instruments for non-destructive, online, or in-situ analyses, playing a pivotal role in green analytical chemistry and sustainable practices. Handheld NIR spectroscopy is critical for developing a circular economy by facilitating the selection of feedstocks for bioenergy and biofuels. It improves sorting accuracy in plastic recycling, contributing to more sustainable practices and addressing plastic waste problems [44]. These devices provide non-destructive, real-time, and in-field data to optimize harvest timing and enhance quality in agriculture. They are used for monitoring moisture content in grains, classifying food powders, detecting adulteration in spices, and assessing the quality of various agricultural products like canola and olives. Bypassing conventional lab-based testing, handheld NIR also makes it possible to quickly identify pesticide residues in fruits. Due to its versatility, cheap cost per test, quick findings, and minimal chemical usage, NIR spectroscopy including handheld versions is ideally suited for environmental applications [45]. It can be applied to in-situ soil organic carbon evaluation and environmentally important research. From textiles to medicines, handheld NIR equipment facilitate quality control and verification, promoting effective supply chains and thwarting counterfeiting. Because of the downsizing, quality control and authentication issues can be handled by non-expert users in daily life. Numerous point-of-use chemical analyses are now possible thanks to recent developments that have produced portable, reliable, and reasonably priced NIR spectrometers that may be integrated into cell phones. This technological progress is crucial for making sustainable analytical methods more accessible and widely adopted [46].

Miniaturized Microextraction Techniques

Solid-phase microextraction (SPME), Dispersive liquid-liquid microextraction (DLLME), and Fabric phase sorptive extraction (FPSE) are microextraction techniques that significantly advance green chemistry and sustainability by reducing solvent use, minimizing waste, and streamlining sample preparation. These methods are highly valued for their efficiency, cost-effectiveness, and environmental friendliness across diverse analytical applications [47].

Solid-Phase Microextraction (SPME) is a simple, highly effective, and green sample preparation technique that integrates sampling, extraction, and concentration into a single, solvent-free step. It aligns with green chemistry principles by eliminating the need for harmful solvents and minimizing waste production, making it a promising technique for eco-friendly alternatives in analytical chemistry [48]. SPME's primary benefit is its solvent-free nature, which solves the problem of waste and contamination associated with most solvent-based analytical procedures. This improves water quality and encourages safer practices by drastically lowering the use of toxic chemicals and organic solvents. It offers a quick, effective, and economical substitute for conventional techniques by combining sampling, extraction, and concentration into a single process [49]. Rapid sample preparation in labs and on-site systems is also made possible by SPME, which integrates automation and boosts productivity without sacrificing accuracy or precision. Particularly in environmental research, SPME can be used to preconcentrate a wide variety of chemicals with different polarity. For the procedure to be as selective and sensitive as possible, the choice of fiber coatings, such as Divinylbenzene (DVB) and Hydrophilic Lipophilic Balance (HLB), as well as their thickness and polarity, are essential [50]. SPME is frequently used to evaluate the quality of water and identify organic pollutants such volatile organic compounds (VOCs), herbicides, and medications. It can assess pollutants from various human activities in water, air, soil, and sediment. Researchers have developed SPME tools incorporating carbon nanotube (CNT) materials to enhance the extraction of pollutants from water and soil, achieving low limits of detection and quantification [51].

Dispersive Liquid-Liquid Microextraction (DLLME) is a new microextraction technique recognized for its simplicity, high enrichment factor, low cost, rapid operation, and minimal organic solvent consumption, making it an environmentally benign sample preparation method. DLLME minimizes the use of organic solvents by forming fine droplets of an extraction solvent in an aqueous sample, which greatly enhances extraction efficiency due to the large surface area contact. This low solvent consumption is a significant advantage over other liquid or solid phase extraction methods. The method provides a high enrichment factor and shorter extraction times, making it efficient for various applications [52]. Recent research in DLLME has focused on using non-toxic or low-toxic extraction and disperser solvents to further align with green analytical chemistry principles. Natural deep eutectic solvents (NADES) are being explored as green alternatives in DLLME. DLLME is widely used in environmental analysis due to its efficiency in extracting analytes from various matrices, including water and soil. It has been successfully applied to determine polycyclic hydrocarbons in water, analyze fungicides in environmental water samples, and extract chemical contaminants in food and water [48].

Fabric Phase Sorptive Extraction (FPSE) is an evolutionary sample preparation approach introduced in 2014 that meets all green analytical chemistry requirements. It is considered a new milestone in microextraction technologies due to its innovative design and environmental benefits. By using a fabric-like sorbent material, FPSE provides a more environmentally friendly option while drastically lowering waste production and solvent consumption. With a high analyte solution concentration, it can guarantee a cleaner extract. To produce a microextraction device with high sorbent loading and quick extraction equilibrium, FPSE creatively blends the advantages of sol-gel coating technology with the rich surface chemistry of different textiles (such as cellulose, polyester, and fiberglass) [53]. Because of its adaptability, FPSE can be directly inserted into original, unaltered samples. A high pre-concentration factor can be achieved without solvent evaporation and sample reconstitution thanks to the strong chemical interaction between the sol-gel sorbent and the fabric substrate, which permits exposure to any organic solvent for analyte elution, usually requiring modest amounts [54]. FPSE is increasingly used for the extraction and determination of various analytes from environmental samples with complex matrices. It has been successfully applied to detect micropollutants, such as pharmaceuticals (e.g., anti-diabetic drugs, anthracyclines) and polycyclic aromatic hydrocarbons (PAHs), in environmental waters. The technique has been adapted for monitoring emerging organic contaminants in environmental water samples and for speciation of heavy metals [55].

Microfluidic and Lab-on-a-Chip Systems

Microfluidic and Lab-on-a-Chip (LoC) systems play a crucial role in promoting greenness and sustainability across various scientific and engineering disciplines. These miniaturized systems offer significant environmental advantages by reducing sample and reagent consumption, minimizing waste generation, and enabling more efficient and portable analytical processes. Microfluidic and LoC systems are inherently green due to their ability to operate with significantly smaller volumes of fluids, often down to nanoliters or even attoliters [56]. By handling minute amounts of liquids, these technologies drastically cut down on reagent usage and sample volumes. This not only lowers costs but also minimizes the generation of chemical and biological waste, aligning with green chemistry principles. The small scale of microfluidic devices often translates to lower energy requirements for operations such as heating, cooling, and fluid manipulation. One significant environmental benefit is the decrease in the creation of chemical and biological waste, which always worries about the disposal of hazardous waste [25]. Microfluidic devices are useful instruments for environmental analysis because they are portable, simple to use, affordable, and have quick reaction times. They have become useful instruments for identifying environmental pollutants such as pesticides, fertilizers, microbes, heavy metals, and per- and polyfluoroalkyl substances (PFAS) in soil matrices, water, and air. For prompt intervention and pollution management, microfluidics makes it possible to monitor a variety of environmental factors quickly and effectively. LoC technologies are creating new opportunities for organismal and environmental research, especially in the areas of biofilm development and microbial interactions, which are critical to environmental health. Nanomaterial-based LoC devices are seeing increased applications in sustainable agri-food industries for various analytical processes [27].

APPLICATIONS IN PHARMACEUTICAL TESTING

Quality Control

Miniaturized systems have found extensive applications across various aspects of quality control, including assays, impurity profiling & dissolution testing. These systems often offer advantages such as reduced sample and reagent consumption, increased throughput, and improved portability [20].

Miniaturized systems, often in the form of micro total analysis systems (μTAS) or lab-on-a-chip (LoC) devices, have significantly impacted biological and chemical assays. By using these methods, researchers may conduct experiments with much less sample volumes and reagent usage, which lowers expenses and waste. For instance, small-volume samples from preclinical species can be used to quantify biotherapeutics utilizing miniaturized immunoassays. High-throughput screening (HTS) in the pharmaceutical sector has embraced miniaturization to speed up research and development and cut expenses. Among these are ultra-high-throughput screening (uHTS) systems, which enable extremely parallel laboratory operations, including the analysis of hundreds of thousands of individual cells or the use of millions of reaction vessels [57]. For cell-based experiments, LoC technology provides accurate control over culturing conditions while concurrently monitoring cell-relevant parameters. For devices that have many layers of co-cultured tissues, precise placement of chemicals such as growth factors or extracellular matrix is beneficial. Compact, quick tests that are essential for early illness diagnosis are made possible by miniaturization, which frequently uses microfluidics to handle tiny volumes precisely. For in-vitro diagnostics and point-of-care applications, highly integrated, reasonably priced microfluidic devices that can perform immunoassays with integrated micropumps and optical biosensors are being developed. Together with surface chemistries, molecular biology, and microfluidics, miniature technologies are developing to provide clear quantitative analysis of complicated biological material, especially for gene analysis in diverse tissues. By combining microelectronics with molecular biology, solution phase experimentation can be made much smaller, allowing biochemical studies to be performed with picoliter sample quantities [58].

Impurity profiling is a critical aspect of pharmaceutical development and quality control, ensuring product safety and regulatory compliance. Miniaturized systems are increasingly being utilized for this purpose. Miniaturized separation methods, such as CE, capillary electrochromatography (CEC), and micro liquid chromatography (μLC), are extensively used in all processes of drug discovery and quality control of pharmaceutical preparations. These systems can provide high efficiency and improved sensitivity in chromatographic separations. Because of their modest flow rates, miniature LC systems make MS coupling easier, allowing for extremely sensitive and thorough impurity investigation. In particular, LC-MS has grown in importance as a technique for detecting drug degradation or reaction byproducts [59]. For radiopharmaceuticals, simplified chromatographic quality control techniques including paper and immediate thin-layer chromatography have been developed, providing ease of use and dependability in assessing labelling effectiveness. Impurity profiling is done using modern analytical methods including UPLC, LC-MS, HRMS, GC-MS, and HPTLC, which are frequently built into small platforms. These hyphenated methods offer impurity separation as well as structural identification [60].

Dissolution testing is essential for evaluating drug release from various dosage forms and ensuring product quality. There are several benefits to smaller systems, particularly when resources are scarce. For low-dose, high-potency medications or in situations where limited formulation is available during the early stages of drug development, miniature dissolving systems are especially helpful [61]. For dissolution testing, these systems may consist of 24, 12, or 96-well plates. A desirable benefit in the early stages of drug development is the ability of compact rotating and stationary disk systems to generate accurate IDR measurements using little amounts of material. To measure disk intrinsic dissolution rates, a new miniaturized intrinsic dissolution screening (MINDISS) assay has been created. For the in vitro dissolving testing of inhalation powders, compact setups have been created that offer high repeatability using tiny quantities of test chemicals and liquids. Miniaturized analytical technologies enable real-time drug dissolution and precipitation testing on a small scale [62].

Bioanalytical Studies

The most important advantages of performing bioanalytical studies using miniaturized systems can be distilled into three key areas.

- *Reduced sample and reagent consumption:* Saving money and preserving valuable or scarce biological samples depend heavily on this. Research on rare specimens that would otherwise be impractical is made possible by miniaturization, which enables investigations with microliter or even nanoliter volumes, making studies financially feasible. This reduces waste and costs, which has a direct effect on research sustainability [47].
- *Increased speed, throughput, and automation:* Miniaturized systems significantly accelerate the analytical process by reducing reaction times and enabling parallel processing of multiple samples. This leads to higher throughput, which is critical for applications like drug discovery and biomarker screening, where large numbers of analyses are required. Automation capabilities inherent in many miniaturized platforms further improve efficiency, reproducibility, and reduce manual labour [46].
- *Enhanced Sensitivity, Specificity, and Portability for Point-of-Care (POC) Applications:* The smaller dimensions can improve the signal-to-noise ratio, leading to better detection limits and the ability to analyze analytes at extremely low concentrations. This is crucial for early disease diagnosis and monitoring. Furthermore, miniaturization facilitates the development of portable devices, enabling immediate on-site analysis outside traditional laboratory settings, which is transformative for point-of-care diagnostics and field-based research [39].

Stability and Degradation Studies

For stability and degradation investigations in pharmaceutical testing, miniature systems provide a number of benefits that make drug development more successful, economical, and perceptive. Significantly lower reagent volumes are used by smaller devices, which lowers expenses and produces less hazardous waste. They are also more environmentally friendly as a result. Because of better heat transmission and shorter diffusion distances, miniature systems provide faster analysis times, which can speed up degradation processes for research. High-throughput screening is made easier by miniaturization, which enables the quick evaluation of a wide range of medication formulations and conditions. This makes it possible to identify ideal formulations and storage conditions more quickly. Degradation studies, like the rapid photocatalytic degradation approach created for phospholipids, can be accelerated by miniature systems, allowing for a quicker evaluation of medication stability. Similarly, the use of elevated temperatures in microcalorimetry can accelerate degradation, allowing analyses to be completed in a reasonable time. Miniaturized systems, especially when coupled with advanced analytical techniques like RP-HPLC, can offer high sensitivity and resolution, enabling the identification of trace levels of degradation products [38]. This offers a more profound comprehension of the pathways and mechanisms of deterioration. Miniaturized devices aid in the early detection of possible stability problems in drug development by facilitating quick screening and thorough analysis. This enables prompt modifications to formulas, packaging, or production procedures, averting future expensive delays and regulatory setbacks. Early formulation development benefits greatly from the use of miniature equipment, which enables scientists to choose suitable excipients and container materials and adjust formulations in response to stress test findings. Greater control over molecular interactions is possible when working at the microscale level, which can shorten the time required for product synthesis and analysis [63]. By offering thorough proof of a drug's stability, shelf life, and storage conditions, the extensive data produced by miniaturized stability studies aids in meeting regulatory criteria. Miniaturized systems support ongoing stability monitoring post-approval, ensuring that the drug remains stable under real-world conditions and across different production batches [64].

Process Analytical Technology

Continuous, real-time monitoring of critical process parameters (CPPs) and critical quality attributes (CQAs) inside the manufacturing process is made possible by miniature sensors and analytical tools. As a result, the "quality-by-testing" paradigm can be replaced with a "quality-by-design" one, allowing for the quick identification of deviations and modifications. Miniaturized Process Analytical

Technology (PAT) sensors give real-time data that enables feed-forward control techniques and feedback, enabling proactive process modifications to maintain ideal conditions and guarantee product quality [65]. The non-destructive analysis provided by many miniature PAT instruments preserves sample integrity and lowers the possibility of contamination because samples do not need to be taken out of the testing procedure. By eliminating the need for manual sampling and analysis, which can be laborious and prone to human error, miniature systems help to boost automation in pharmaceutical testing. This automation streamlines workflows and enhances efficiency. At-line, On-line, and In-line *Analysis:* Miniaturized platforms enable the implementation of at-line, on-line, and in-line analytical methods, shifting away from traditional off-line laboratory testing. This brings the analytical laboratory closer to the sample, accelerating analysis and decision-making [66].

The small footprint of miniaturized devices makes them suitable for integration into various manufacturing environments, including small-scale and multi-purpose platforms, and can even facilitate remote operation. Hand-held instruments, for example, have become feasible due to miniaturized spectrometers. Miniaturization significantly reduces the volume of samples and reagents required for analysis, leading to cost savings and reduced waste. This is particularly advantageous for expensive or limited materials in biopharmaceutical production. Numerous parameters, including temperature, dissolved oxygen, electrical conductivity, glucose, lactate, and cell density, can all be measured simultaneously using contemporary miniaturized PAT sensors [67]. This multi-parametric capacity offers a thorough comprehension of the state of the process. Initiatives for the next generation envision microanalytical gadgets that leverage wireless connectivity to improve capabilities and function inherently safely. Critical quality attributes can be monitored in real time without causing any damage thanks to miniature spectroscopic technologies like Raman and near-infrared (NIR) spectroscopy. They are employed for purposes like tracking the distribution of particle sizes, medication content, and blending homogeneity. In order to lower treatment costs, portable and miniature microfluidic chip biosensors are being developed for online PAT monitoring of particular chemicals. Point-of-care testing and self-monitoring are being conducted using tiny, screen-printed electrode sensors [57] (Table 2).

CHALLENGES AND FUTURE PERSPECTIVES

Implementing miniaturized systems in pharmaceutical testing, while offering numerous advantages, also presents several challenges and limitations that need to be addressed for their widespread adoption.

Technical and Operational Hurdles

- *Clogging:* A significant problem in miniaturized systems is clogging, particularly at the points where reagents are added to test wells. This can disrupt assays and affect data reliability [68].
- *Evaporation:* Evaporation of reagents, especially in sub-microliter volumes, is another challenge that can lead to timing issues and inaccurate results in miniaturized tests [69].
- *Column Overloading in Miniaturized LC systems:* In miniaturized liquid chromatography (LC) systems, column overloading is a common issue due to significantly reduced injection volumes. This can negatively impact peak symmetry and chromatographic resolution (68).
- *Fluid handling:* Fast, precise, accurate, and controllable fluid dispensing is crucial for the performance of ultra-high-throughput screening (uHTS) assays, and achieving this in the submicroliter range remains a key engineering challenge (68).
- *Interfacing with the outside world:* Interfacing between miniaturized equipment and the external environment is not as straightforward as it might seem. This includes challenges with hardware and connections, such as the use of smaller and varied threaded fittings in miniaturized chromatography systems, which can lead to confusion and frustration (69).
- *Maintaining Signal-to-Noise Ratio:* Overcoming assay miniaturization challenges involves maintaining an optimal signal-to-noise ratio while ensuring transferability to larger-scale operations [70].

- *Sample volume limits:* Determining the realistic lower limit for sample volume is a key issue for the future implementation of microminiature analyzers (70).

Table 2. Summary of miniaturized methods used for various drug types [57–67].

Miniaturized Technique	Principle / Type	Pharmaceutical Application	Advantages / Key Features	Selected References / Examples
Micro-HPLC (μHPLC)	Miniaturized liquid chromatography using narrow-bore columns	Quantification of APIs and impurities in formulations	Reduced solvent and sample use; faster analysis; high sensitivity	Used for assay and stability testing of antibiotics and NSAIDs
Nano-LC / Capillary LC	LC using nano-scale flow rates	Bioanalytical quantification of drugs in plasma	High efficiency; compatibility with MS detection; low sample volume	Applied in pharmacokinetic studies
Micro-GC	Gas chromatography on a miniaturized chip or capillary system	Analysis of volatile impurities and residual solvents	Portable, rapid separation, low power consumption	On-site solvent analysis in manufacturing
Capillary Electrophoresis (CE)	Separation based on charge and size in a narrow capillary	Chiral separation, impurity profiling, drug purity testing	Minimal reagent use; rapid analysis; high resolution	Common in enantiomeric purity testing
Microchip Electrophoresis (MCE)	Lab-on-a-chip CE system	Small molecule and metabolite separation	Integration of separation and detection; ultra-fast results	Suitable for point-of-care and QC screening
Solid Phase Microextraction (SPME)	Fiber-based microextraction without solvents	Sample preparation for volatile and semi-volatile drugs	Solvent-free, simple, reusable, eco-friendly	Used for residual solvent and flavor analysis
Dispersive Liquid–Liquid Microextraction (DLLME)	Miniaturized LLE using small dispersive solvent volumes	Preconcentration of drugs/metabolites before analysis	High enrichment factor; rapid extraction	Applied for bioanalytical quantification of drugs
Fabric Phase Sorptive Extraction (FPSE)	Hybrid sorptive microextraction using fabric substrates	Extraction of pharmaceuticals from aqueous and biological samples	Simple, solvent-free, reusable; green alternative	Used for antibiotics and NSAID extraction
Stir Bar Sorptive Extraction (SBSE)	Stir bar coated with sorbent for analyte extraction	Trace analysis of drugs and degradation products	High sensitivity; no solvent; reusable	Applied in stability and impurity testing
Microfluidic Devices / Lab-on-a-Chip	Integration of analytical steps (sample prep, separation, detection) on a microchip	On-site drug content and purity testing	Portable, automated, low sample/solvent use	Used in real-time quality control (PAT tools)
Micro-ATR–FTIR / Micro-Raman	Miniaturized spectroscopic detection systems	Solid-state characterization, polymorph analysis	Non-destructive, fast, minimal sample	In-process identification of raw materials
Portable NIR Spectroscopy	Diffuse reflectance spectroscopy in handheld format	Rapid API quantification, tablet content uniformity	Real-time, non-destructive, field-deployable	Used in PAT and raw material testing

Economic and Commercialization Challenges

- *Cost of manufacturing:* The cost of miniaturized systems is strongly linked to the manufacturing volume. Producing devices at scale often requires developing custom procedures to replace manual assembly with automation [71].
- *Investment in validation:* Developers and suppliers of microphysiological systems (MPS) need to weigh the investment required to validate their technology against the potential market size. This often limits the development of MPS platforms to those with a viable business proposition [72].

- *Lack of standardization:* There is a lack of standardized production protocols for certain components, such as hydrogels used in cell scaffolds, leading to high variability. This absence of agreed-upon "gold standard" validation metrics for MPS systems or the cells and tissues within them poses a significant regulatory hurdle [73].
- *Market adoption:* Despite the disruptive potential of MPS technology, widespread adoption has been limited by a gap in translation between platform developers, end-users, regulatory agencies, and the pharmaceutical industry. Pharmaceutical companies are generally considered mid to later-term followers of this technology [74].
- *Business case and niche:* The business case for each supplier differs based on the targeted stage of the drug development process and the specific solution or niche offered. Early engagement with biotechnology industry members and end-users is crucial to assess open fields of application and avoid developing technology without a specific need [75].

Regulatory and Acceptance Issues

- *Regulatory hurdles for MPS:* Microphysiological systems (MPS) face significant regulatory hurdles, including the need for validation and qualification by regulatory agencies. There is currently no agreed-upon "gold standard" for validating MPS systems [68].
- *Context of Use (CoU) definition:* Clearly defining the "Context of Use" for each MPS platform is critical for pushing the maturity of these technologies. The pharmaceutical industry needs to qualify MPS systems for specific contexts of use and assays [69].
- *Data submission concerns:* In the US, there is caution among those considering Investigational New Drug (IND) applications regarding potential delays in approvals for data packages that include MPS data. Regulators have noted that very little to no MPS assay data has been submitted so far [72].
- *Need for validation and standards:* Regulatory bodies require additional validation and standards development to overcome adoption hurdles. The IQ MPS Affiliate has identified impediments to MPS adoption, including the need for standards development and adequate amounts of robust and reproducible data to increase technological confidence [70].

Scientific and Biological Considerations

- *Cell sourcing and variability:* Creating robust, reliable, and reproducible MPS platforms requires cells that meet high-quality metrics. However, primary cells are often difficult to collect, finite in amount, and show variability between collection sites. Human induced pluripotent stem cell (hIPSC) technology, while promising, is relatively novel and faces challenges such as variability in differentiation protocols and potential "epigenetic memory" of donor tissues. Commercial cell lines, while easier to use, can be immortalized, potentially leading to biologically inaccurate or incomplete data [75].
- *Cell scaffolds and fabrication materials:* Cells require specific scaffolds or extracellular matrices for proper architecture and function, but hydrogels used for this can be difficult to engineer and show high variability. The materials used to fabricate the chips themselves, such as polydimethylsiloxane (PDMS), can absorb small hydrophobic molecules (drugs), affecting drug concentration [73].
- *Platform integration:* Integrating individual MPS systems to assess human systemic responses presents challenges. While functional coupling is technically flexible, it does not mimic native physiological flow. Physical linkage requires careful attention to sterility, common media, and organ scaling. Challenges also include inhibiting air bubble formation, maintaining sterility during coupling, preventing fluid leakage, and controlling flow rate and oxygenation levels among different organ systems [75].
- *Complexity of models:* The complexity of an MPS model can be a limiting factor, and not all criteria outlined in qualification checklists will be satisfied in a single model [72].

Miniaturized systems are poised to play a central role in the future of sustainable and high-performance analytical chemistry within pharmaceutical testing. Their continued development is driven

by the demand for faster, more accurate, and cost-effective methods across various stages of drug development and quality control [74].

Advancements in Miniaturization Technologies

- *Continued miniaturization:* The trend toward miniaturization will persist, fueled by advancements in nanotechnology, flexible electronics, and bio-integrated sensors. This will enable even smaller and more powerful devices for pharmaceutical applications [57].
- *Integration of Artificial Intelligence and Machine Learning:* A prominent future trend is the integration of artificial intelligence (AI) and machine learning (ML) to optimize various aspects of miniaturized systems, including column design and separation processes. AI is expected to transform pharmaceutical stability testing by predicting shelf life, accelerating studies, and automating inspections [73].
- *Smartphone-Based Spectroscopy:* The development of smartphone-based spectroscopy is a key market trend for miniaturized spectrometers, enabling portable and accessible analytical capabilities [74].
- *3D Printing for Tailored Devices:* Three-dimensional printing (3DP) is transforming the development of miniaturized devices, especially for point-of-care testing (PoCT). This technology allows for the creation of compact, portable, and patient-specific diagnostic devices, enhancing diagnostic speed, accessibility, and personalization. Future directions include the integration of AI, the Internet of Things (IoT), and multifunctional capabilities into 3D-printed devices [73].
- *Microfluidics and Lab-on-a-Chip Systems:* Microfluidic and lab-on-a-chip systems will continue to advance, offering enhanced capabilities for sample preparation, separation, and combinatorial synthesis. These systems allow for highly controlled reaction environments, enabling faster analysis, reduced reagent consumption, and the exploration of new drug entities [69].

Enhanced Applications in Drug Development and Testing

- *Drug discovery and development:* Miniaturized assays are transforming drug discovery by enabling high-throughput screening with reduced reagent volumes, increased efficiency, and improved accuracy. Microfluidics will make ex vivo testing possible in in vivo-like environments, opening new avenues for drug discovery [68].
- *Stability and degradation studies:* Miniaturized techniques will continue to improve the efficiency, accuracy, and predictive capabilities of stability testing. This includes the development of miniaturized, high-throughput assays for screening drug-polymer formulations to predict stability. Microcalorimetry, with its ability to monitor reactions at various temperatures and its high sensitivity, will continue to be a technique of choice for characterizing the stability of pharmaceutical compounds [71].
- *Quality Control (QC) testing:* Microfluidic quality control systems are gaining increasing attention for radiopharmaceuticals due to reduced sample and reagent consumption, shorter analysis times, higher detection sensitivity, and multiplexing capabilities. This will help address the challenges of testing short-lived radiopharmaceuticals within limited timeframes [44].
- *Personalized medicine and Point-of-Care testing:* Miniaturization is a significant driver for personalized medicine. The production of small, fast, and easy-to-operate devices for point-of-care (POC) or even household testing will become more widespread, enabling broader monitoring of health parameters and biomarker tracking. Miniaturized biosensors, particularly those developed through 3D printing, will play a crucial role in improving access to diagnostics and facilitating earlier disease detection [73].

Addressing Challenges and Overcoming Limitations

- *Improved material standardization and regulatory clarity:* Future efforts will focus on addressing challenges such as material standardization and regulatory hurdles, especially for 3D-printed devices and micro-physiological systems. Better alignment between the regulatory controls of pharmacogenetic tests and drugs is also needed [68].

- *User-Friendly interfaces:* The development of user-friendly interfaces between humans and microchips will be crucial for the long-term success and widespread adoption of microminiature analyzers [76].
- *Solving scalability issues:* Strategies to address challenges in scaling miniaturized pharmaceutical systems, such as issues with vortex formation, changed volume dynamics, and wall effects in miniaturized bioreactors, will be a focus of future research. Miniaturized, modular, and continuous manufacturing processes are expsected to help speed up scale-up and address supply chain complexities [77–80].

CONCLUSION

Miniature analytical procedures greatly improve green and sustainable pharmaceutical testing as they use fewer resources and have less of an impact on the environment. In line with the tenets of green analytical chemistry, these techniques minimize the use of dangerous chemicals and solvents, produce less waste, and use less energy. Miniaturized systems make it possible to prepare and analyze samples more effectively with fewer volumes, which makes drug testing more economical and environmentally friendly. Additionally, through enhanced analytical performance, accelerated analysis times, and greater throughput, miniaturized analytical techniques improve the effectiveness of pharmaceutical testing. Rapid screening, accurate measurements, and real-time monitoring are made possible by the incorporation of cutting-edge technologies like microfabrication, automation, and AI into these systems. This speeds up drug development and quality control. This efficiency not only streamlines laboratory operations but also supports the early identification of potential drug candidates and the robust assessment of pharmaceutical quality, making the entire testing process more productive and reliable.

Conflict of Interest

The author declares no conflict of interest.

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