Review article

Recent microfluidic applications in Pharmaceutical Sciences and its potential utility in bottom-up concepts of Quality by Design

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SUMMARY

Introduction: Microfluidic science has significantly permeated biomedical sector since the 1990s, today they have potential application in quality-based design of pharmaceutical products using bottom-up approaches. **Methodology:** In this article, a review of some articles published from 2019 to 2025 is made to show the utility that microfluidics can have in each stage of medicines development. To demonstrate the capabilities of micro systems some examples are summarized, highlighting the qualities that may be attractive from the Quality by Design (QbD) methodology point of view; In order to segment the information, the topics are classified into four groups: medical diagnosis, production of drug delivery systems, drug discovery and organ-on-a-chip technology. **Results:** Since microfluidics make it possible to produce different types of nanostructured formulations and control their final properties, when increasing the conceptual basis on the mechanisms of diseases and evaluate the effect of drugs when exposed to human cells, it is possible to spread its potential in an integral way to all development phases of pharmaceutical products.

Keywords: Microfluidics; medical diagnostics; drug delivery system; drug discovery; Organ-on-a-chip; Quality by Design; bottom-up approach.

RESUMEN

Aplicaciones recientes de microfluidos en las ciencias farmacéuticas y su utilidad potencial en conceptos "abajo-hacia-arriba" asociados a la Calidad Desde el Diseño

Introducción: La ciencia de microfluidos ha permeado de forma importante al sector biomédico desde 1990, hoy en día tienen aplicación potencial en el diseño de productos farmacéuticos basado en la calidad, mediante el enfoque de abajo hacia arriba. **Metodología:** En este artículo se hace una revisión de algunos artículos publicados desde 2019 hasta 2025 con la finalidad de mostrar la utilidad que pueden tener los microfluidos en cada una de las etapas del desarrollo de medicamentos. Para demostrar las capacidades que tienen las microplataformas se resumen algunos ejemplos destacando las cualidades que pueden ser atractivas desde el punto de vista de la metodología de Calidad desde el Diseño (QbD). Con la finalidad

de segmentar la información, se clasifican los temas dentro de cuatro grupos: diagnósticos médicos, producción de sistemas de liberación de fármacos, descubrimiento de fármacos y tecnología de órgano-en-chip. **Resultados:** Dado que los microfluidos permiten producir diferentes tipos de formulaciones nanoestructuradas y controlar sus propiedades finales, al incrementar las bases conceptuales sobre los mecanismos de las enfermedades y evaluar el efecto de los medicamentos al exponerlos a células humanas, es posible extender su uso de forma integral a todas las etapas del diseño de productos farmacéuticos.

Palabras clave: Microfluidos; diagnósticos médicos; sistemas de liberación de fármacos; descubrimiento de fármacos; Órganos-en-Chips; Calidad desde el Diseño; aproximación "abajo-hacia-arriba".

RESUMO

Aplicações recentes da microfluídica nas Ciências Farmacêuticas e sua potencial utilidade em conceitos bottom-up de Qualidade por Design

Introdução: A ciência da microfluídica permeou significativamente o setor biomédico desde a década de 1990 e, atualmente, apresenta potencial aplicação no design baseado na qualidade de produtos farmacêuticos, utilizando abordagens bottom-up. **Metodologia:** Este artigo apresenta uma revisão de artigos publicados entre 2019 e 2025 para demonstrar a utilidade da microfluídica em cada etapa do desenvolvimento de medicamentos. Para ilustrar as capacidades dos microssistemas, alguns exemplos são resumidos, destacando as qualidades que podem ser atrativas sob a perspectiva da metodologia de Qualidade por Design (QbD). Para segmentar as informações, os tópicos são classificados em quatro grupos: diagnóstico médico, produção de sistemas de liberação de fármacos, descoberta de fármacos e tecnologia de órgãos em chip. **Resultados:** Como a microfluídica possibilita a produção de diferentes tipos de formulações nanoestruturadas e o controle de suas propriedades finais, ao ampliar a base conceitual sobre os mecanismos das doenças e avaliar o efeito de fármacos quando expostos a células humanas, é possível estender seu potencial de forma integral a todas as fases de desenvolvimento de produtos farmacêuticos.

Palavras-chave: Microfluídica; diagnóstico médico; sistema de liberação de fármacos; descoberta de fármacos; órgão-em-um-chip; Qualidade por Design; abordagem bottom-up.

1. INTRODUCTION

Microfluidics are defined as the discipline responsible for studying fluid behaviors when they circulate in confined spaces at microscopic scales; this branch of the fluid mechanics had origin in the 1980s thanks to the advances in miniaturization for micro electro-mechanical systems (MEMS) which spread to another areas of knowledge (chemistry, biology, medicine) since 1990s [1]. In the last decades this field has permeated toward different topics in pharmaceutical sciences which, in the current article, are classified into four general groups: Medical diagnosis, production of micro/nano platforms, drug discovery, and organ-on-a-chip (OoC) technology.

Since microfluidic science approaches are given at submillimeter scale, it could be a powerful tool for products design by means of bottom-up theories. Those concepts imply a thorough understanding of the micro and nanoscale events influence on the product desired property; it is believed that a systematic integration of multiple disciplines to model complex phenomena will lead to translating the molecular processes into phenomenological equations to create and control functionalities through the manufacturing process. This group of concepts is framed in what is described in the literature as *le Genie du triple "processus–produits–procédé"* (the triplet molecular processes–product–process engineering) [2]

Some recent proposals in scientific literature mention the importance of applying emergent concepts into general and accepted methodologies for drug design and development that is the case of QbD which has been accepted by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) since 2009.

It is mentioned in the article written by Colombo *et al.* [3] the concern about high failure rates in nanopharmaceutical research and development due to the incipient bottom-up strategies for products manufacture which lead to an inappropriate control of quality attributes. In that order of ideas whether one study microscopic phenomena throughout micrometric technology (microfluidics, particularly), it is possible to improve designs, process control, and parameter predictability. In his words there are "emerging opportunities in the synergistic implementation of QbD strategies and microfluidic production in contemporary development and manufacturing of nanopharmaceuticals".

The foundations of *Quality by Design* (QbD), based on knowledge and risk management, support the development of systems that incorporate microfluidic studies. The creation of functional microstructures—grounded in the understanding of material properties at the microscale, the identification of critical quality attributes (CQAs), and the definition of manufacturing processes based on critical process parameters (CPPs) in the microscale represent a challenge of establishing a robust design space. This approach enables the development of functional products through a bottom-up design strategy, where desired properties emerge from the structure and behavior at the microscale.

As a consequence of the microfluidics unique features such as short analysis time, low reagents consumption, accelerated mass and heat transfer, parametric control, profitability, possibility of integrating complementary technology *in situ*, ability to incorporate advanced cell cultures, and so on, it has demonstrated potential to improve lifecycle in products development, medical diagnosis efficiency, safety and toxicity characterization, drug-cells and cell-cell interaction comprehension, disease mechanistic understanding and human response predictability. All these qualities make it a powerful tool that could contribute significantly to medicines development with the aid of QbD because the aforementioned methodology is based on concepts that seek to integrate knowledge about safety, efficacy, bioavailability, stability, process engineering, risk assessments, and control strategies with the purpose of materializing high-quality products supported on solid basis.

Based on the need to publicize the importance of microfluidics in the pharmaceutical world, in this article are discussed some microfluidic applications in pharmaceutical sciences shown in papers from 2019 to 2025 with the purpose of evidencing its potential as a support tool for the design of biologically active products into the QbD and bottom-up frames.

2. MICROFLUIDICS IN MEDICAL DIAGNOSIS

Microfluidics technology can be applied for the early diagnosis of different diseases and hard threatening conditions, for example, malignant tumors or nosocomial infections. Microfluidic devices have sparked interest in the scientific community due to their advantages over laboratory conventional methodologies for samples analysis. Miniaturized systems provide high sensibility, short analysis times, are less prone to human errors, and they could be economically feasible since the amount of reagents and samples are lower [4].

For diseases diagnostics, researchers have explored the possibility of developing high sensibility and accuracy biosensors with the purpose of perform biochemical analysis with the same reliability of a laboratory assay [5]. A series of sensors have been elaborated with the aid of microfluidics technologies, which allow their application in a wide variety of diagnostic

assays [6, 7]; among the physical phenomena, optic, electronics, microwaves and radiofrequencies are the most used in sensors [5]. The following discusses several scientific articles aimed at demonstrating the potential and possibilities that microfluidics offers in disease diagnosis:

Lu *et al.* [8] were able to craft a microfluidic device with the potential to early diagnose cholangiocarcinoma. According to the authors, one of the drawbacks related to the diagnosis of this disease is the variety of biological material that can lead to wrong results or even false positives. In those cases, microfluidic platforms can increase interactions between molecules and the intrinsic processes in biochemical analysis could be automated. The microfluidic chip designed by Lu *et al.* consisted in three layers of polydimethylsiloxane (PDMS) and one layer of polycarbonate (PC) coated with PDMS, linked together by a plasma oxygen treatment. The design of the device was conceived to carry out extraction, isolation, and cancer cells staining; to do so, it was necessary to integrate micro elements such as micropumps, micromixers, reservoirs, microvalves, and microchambers with reagents. In general, the working principle of the microdevice falls into four steps: (1) bile fluid incubation, (2) isolation of tumor cells by magnetic pearls coated with affinity reagents, (3) washing and removal of unbounded cells, (4) Addition of antibodies and a special reagent for the cell staining. The microfluidic chip developed by Lu *et al.* is shown in Figure 1:

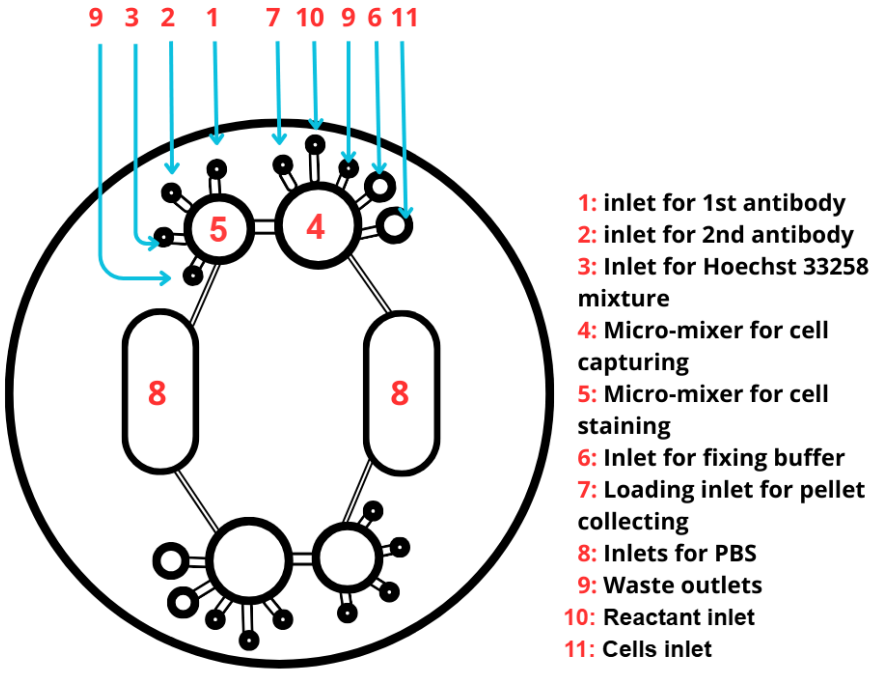

Figure 1. Graphical representation of the microchip for cholangiocarcinoma diagnostic. Adapted from Ref. [8].

In addition, Maji *et al.* [9] demonstrated that a microfluidic device has the potential to be used in platelet loss diagnostic during a traumatic hemorrhage. This research is relevant because a fast platelet count and their effect in the hemostatic process is valuable if it is necessary to implement strategies to mitigate trauma-induced coagulopathies. Despite there are laboratory assays to monitor patient's health, access to appropriate instrumentation is not always possible and thus it could not be carried out the corresponding analysis. In that order of ideas, it would be useful to have a miniaturized system which integrates analytical techniques to track patients' health rapidly. The microfluidic chip (shown in figure 2) developed by Maji *et al.* is

based on qualitative measurements by dielectric spectroscopy; this technique allows the quantification of a material relative dielectric permittivity, a useful property to detect cellular and non-cellular abnormalities in hemostatic processes. Results obtained by Maji *et al.* show that analytical determinations by dielectric spectroscopy have potential to provide information about hemostatic imbalances. In general, the analysis of blood composition is of interest for various biomedical applications and disease diagnostics; for this reason, Ma *et al.* [10] developed a microdevice capable of separating cellular components from blood plasma using acoustic radiation.

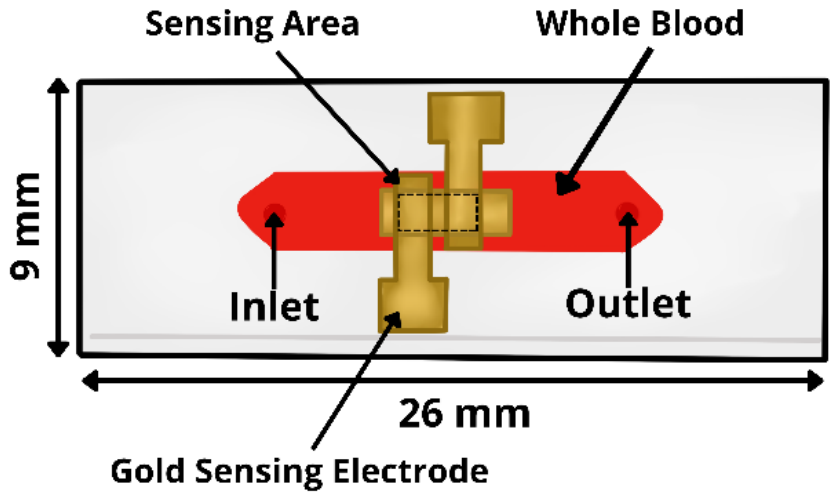

Figure 2. Prototype of microfluidic device for monitoring platelet loss during traumatic hemorrhages.

The study conducted by Fang *et al.* [11] demonstrated the advantages of microfluidic systems in fast physiopathology diagnostics. In that research a microfluidic based device was developed to detect sepsis, a potentially mortal disease derived from the immune response towards bacterial, fungal, or viral infections. This condition requires a rapid and accurate diagnostic with the purpose of provide drugs in a timely manner. According to Fang *et al.*, a conventional sepsis diagnostic needs a blood culture which takes 48 to 72 hours, followed by a bacterial identification assay. To solve this problem, researchers proposed the integration of microfluidic elements which allow separation of microorganisms from blood and a specific bacterial isolation. To achieve the desired diagnostic, a two-chip system was developed; the first is responsible of sample pretreatment, inside their microchannels is found a micropillar structure which deviate particles larger than 3 - 4 μm; the second chip is constituted of special microchambers loaded with magnetic particles coated by mannose-binding lectin. The microparticles and the bacterial isolated sample are transferred to a micromixer, later the bacteria – pearl complex is recollected by a magnet. Experiments developed in the study suggest that microsystems have potential to diagnose sepsis in a few hours.

Microfluidics have been also applied in research projects derived from the COVID-19 pandemic. Kim *et al.* [12] developed an innovative method to detect SARS-CoV-2 by using a mesh-based system which contain microfluidic pores. The working principle of that device can be summarized in the following manner: There are two chambers connected by a microchannel. In one of them is loaded the sample; the second is sealed by a rubber stopper. Due to pressure effects, the sample will not be transferred to the second chamber. Once the stopper is perforated, there are two possibilities: (1) the sample flow towards the empty chamber or (2) the sample will keep static. Since there is a conjugated mesh which can form a DNA hydrogel, the

sample behavior depends on the presence of the pathogen. If the pathogen is present in the sample, the hydrogel will clog the membrane pores and subsequently, the liquid stays static in the first chamber. Otherwise, the liquid will be transferred to the second reservoir. When operating conditions are optimized, it is possible to reach a detection limit of 3 aM with an analysis time of 15 minutes or a detection limit of 30 aM with an analysis time of 5 minutes. A more recent study related to the detection of this disease is presented by Nguyen *et al.* [13]. In this article, a microfluidic platform was developed that integrates electronic elements and a series of microreactors, allowing remote manipulation of fluid control, temperature control, fluorescence detection, and data analysis. This device is essentially a micro-laboratory aimed at maximizing the automation of procedures required for disease detection based on the reverse transcriptase-loop-mediated amplification (RT-LAMP) assay.

Other researchers like Zhu *et al.* [14] have worked in novel technology development which can be applied in microsystems with the aim of diagnose potential mortal diseases for healthcare workers. Their proposal is a "lightweight and flexible multiplexing harmonic transponder sensor, which allows for rapid, *in situ* detection of at least two types of liquid samples" [14]. In summary, the devised microdevice consists of a transceiver which transmits a constant intensity frequency to a multiplexed harmonic sensor. The signal is received by an antenna, and the intensity is modulated through the sample analyzed within the microchannels. Received signals can be retransmitted to a specific receptor such a cellphone. Radiofrequency-based technology has the capacity of monitoring liquid properties rapidly, without direct contact, and in noisy environments.

Microfluidics have also paved the way to new methodologies in cancer research. According to Silva *et al.* [15] "microfluidic devices have emerged as promising tools for research and applications in oncology, because the manipulation of small volumes of liquid is ideal for tumor cell sorting from biofluids or liquid cultures, and the development of 2D and 3D cell culture models for cancer cell, allows the migration/metastasis studies and drug screening, as well as the design of sophisticated drug delivery systems". In microfluidic cancer diagnostic field, circulant tumor cell analysis is a popular and well accepted technique because it have demonstrated to be useful in understanding, diagnose and treat different types of cancer [15, 16].

To identify cancer cells, it is required to use cell manipulation techniques which are based on microfluidic devices; among those techniques it is found the cell isolation. Tavakoli *et al.* [16] state that "single cell isolation is crucial to single-cell analysis in order to better understand the variations from cell to cell, which can provide valuable information for diagnostics and other biomedical applications". In that order of ideas, microfluidic technologies have a relevant role in producing platforms which could manipulate cells precisely by entrapment, transport, and cell delivery. In scientific literature, studies have been reported about a few entrapment methodologies such as mechanical traps and microfluidic droplets. Below are discussed the methodologies and some related examples.

Mechanical traps are based on the use of microstructures such as microwells, microreservoirs, microvalves, among others. In a microsystem intended for the diagnosis of cancer, combinations of these microstructures and variations in geometry, size, and configuration can be found, resulting in a wide variety of studies that show different yields in the cell isolation process. To mention a few examples, we have the study by Tu *et al.* [17] in which the capture of cells is carried out in a microsystem that contains triangular microwells; Rho *et al.* [18] designed a V-type valve to improve the handling of particles of different sizes in microdevices, proving to have potential application in single cell analysis; Armbrecht *et al.* [19] developed a microfluidic chip capable of capturing, monitoring, and analyzing single cells. In this study,

hydraulic traps were used that allow static cells to be kept in a specific position within the microdevice, thus facilitating automated cell analysis.

Droplet-based cell capture technologies consist in the formation of compartments (represented by droplets) that can isolate cells individually for subsequent storage, identification, and transport [16]. Isolation using microdroplet technology has been commonly performed by applying T-type microstructures where the dispersion of two phases immiscible with each other is made; however, the need to form droplets of specific sizes and characteristics has implied the development of microplatforms that use external actuation techniques, including electrical, magnetic, optical, thermal controls, among others [16].

Isolation of cancer cells in microsystems can also be carried out by applying knowledge in antibody-antigen interactions and targeting epithelial cell adhesion molecules because this surface antigen is overexposed in almost all types of cancer [15]. In this sense, the investigations that use this theoretical foundation of antibody-antigen interactions focus on the functionalization of micro-devices with different types of antibodies that bind to the specific antigens of the cells of interest. Some examples in the scientific literature include the functionalization of microsystems for the detection of lung cancer [20], pancreatic cancer [21], colon cancer [22], breast cancer [23], ovarian cancer [24], and gastric cancer [25].

The application of microfluidic science in cancer diagnosis has gained increasing interest in recent years; this can be demonstrated by searching in Scopus database the keywords “Microfluidics” and “Cancer diagnostic” (see Figure 3).

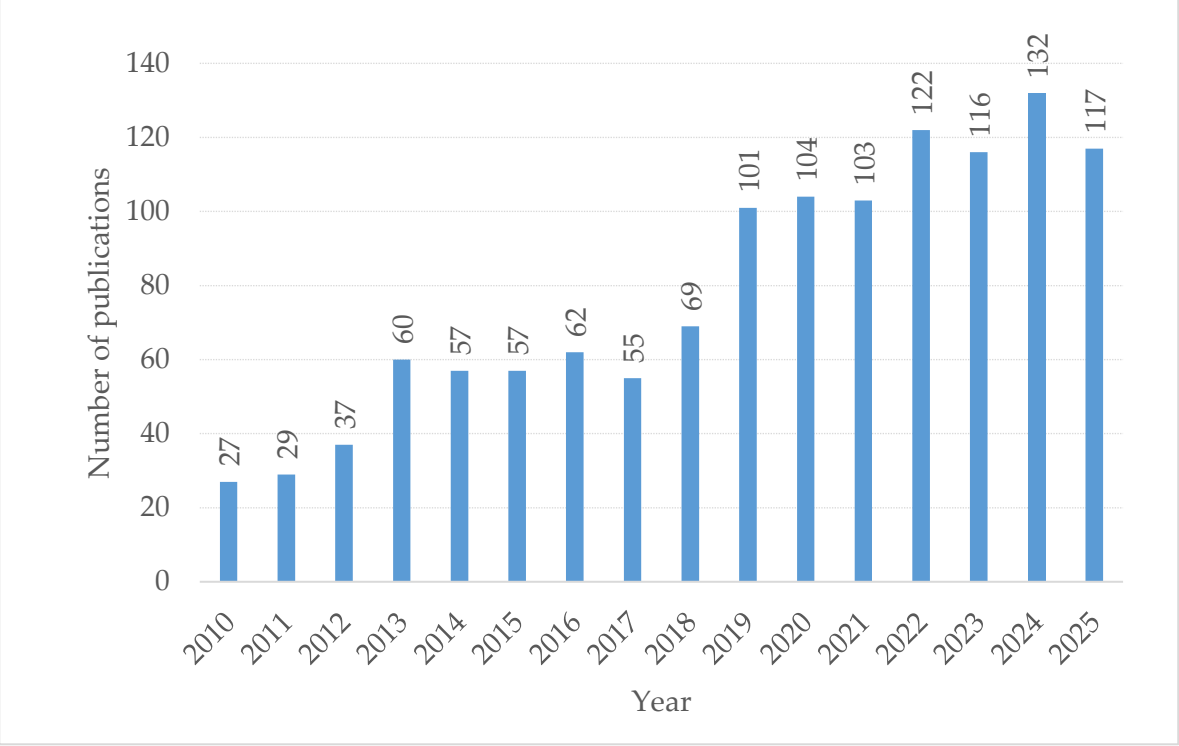

Figure 3. Search results in Scopus database, using the keywords "Microfluidics" and "Cancer diagnostic". The data was obtained in September 2025.

Research related to cancer diagnosis is based on the study of biomarkers such as circulating cells, cell-free DNA and extracellular vesicles; Additionally, there is a wide variety of methodologies based on microfluidics that allow the isolation of these biomarkers, including immunoaffinity, filtration, acoustofluids, viscoelastic flow, and electrokinetics [26]. Some of these methodologies are discussed in depth in review articles published along the last years, such is

the case of the document published by Yang *et al.* [27]. This paper also discusses other methods for diseases detection caused by viruses and bacteria through the use of microsystems made of materials such as PDMS (polydimethyl siloxane), paper or other polymeric materials, and incorporating technological elements such as sensors that can be connected to smartphones to carry out diagnoses with a certain level of speed.

The potential of microfluidics in the field of medical diagnostics lies in its ability to provide deeper insights into the underlying mechanisms of various diseases. This understanding can be leveraged to design more effective therapeutic strategies. As a result, microfluidics supports the development of better-informed pharmaceuticals and enables the identification of critical quality attributes that must be addressed to meet patient expectations and regulatory standards.

3. MICROFLUIDICS IN CONTROLLED RELEASE SYSTEMS

In recent scientific literature, a broad variety of studies can be found about microfluidic chips with different structures such as microchannels, microvalves, micromixers and other microscopic elements that allow the production of micro and nanoplatforms (for pharmaceutical and cosmetic applications) with well-defined physicochemical properties. In the following paragraphs, some newest applications of microfluidics to obtain pharmaceutical and cosmetic formulations will be discussed, as well as some relevant conceptual aspects in each case.

One advantage of microfluidic technology compared to conventional mass production methods is the ability to continuously produce formulations with precisely controlled morphological characteristics. However, it should be considered that obtaining nanoparticles in reduced spaces can cause clogging and failure of the microelements incorporated into the system. For that reason, Bolze *et al.* [28] mention that the use of active mixers (that is, those that involve the addition of power from external sources) in microsystems can reduce the clogging probability.

Among the variety of active mixers (rotors, magnetic or electric fields, acoustic waves, etc.), the authors of the article selected ultrasound as the external energy source to enhance the continuous production of trimyristin lipid nanoparticles by the nanoprecipitation method. In this investigation, experiments were carried out to verify the ultrasound effect in nanoparticles production and it was found that when mixing the fluids (solvent, antisolvent and an auxiliary current whose purpose is to improve mixing efficiency) without ultrasound, a supersaturated solution remains in contact with the internal walls of the microchip, which favors precipitation and as a consequence of this, obstructions occur within the microchannels, thus generating leaks in the seals before having completed 5 minutes of operation. When the system is subjected to ultrasonication, it is possible to carry out the production of lipid particles from 4 to 7 hours until the appearance of leaks in the system seals. Bolze *et al.* [28] suggest that ultrasonication has a cleaning action thanks to a combined effect of cavitation and inertial effects that are caused by rapid movements within the microchip. Finally, it is worth highlighting the fact that in this article the effect of the frequency of acoustic waves on particle size and polydispersity was not thoroughly evaluated, therefore, it is expected a study that incorporates these conceptual aspects. A schematic of the microfluidic chip used by Bolze *et al.* [28] is shown in Figure 4:

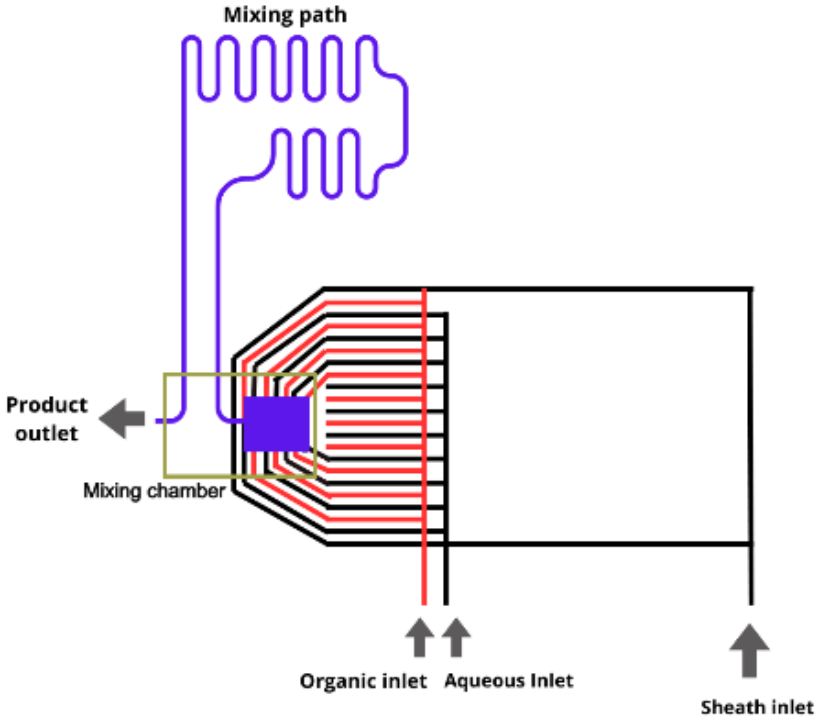

Figure 4. Schematic of the chip configuration used by Bolze *et al.* [28].

Other research that uses microfluidic science for the continuous production of pharmaceutical formulations is made by Patil *et al.* [29]. In this study, luliconazole-loaded microemulsions were obtained and the process parameters that significantly influence droplet size and polydispersity were identified, which in turn determine reproducibility, stability, and effectiveness in *ex vivo* permeation assays. The experiments carried out by the authors allowed us to compare the droplet sizes obtained when processing by a batch methodology and by microfluidics (a schematic of the chip structure developed by the authors is shown in Figure 5). Unlike the article by Bolze *et al.* [28], in this case passive micromixers are used, that is, geometries and microelements that do not require an external energy source to favor the fluids mixing process. Nonetheless, the two studies agree that the precise control of the internal mixing of the raw materials is decisive in the quality characteristics of the product and that, for this reason, traditional batch production methods fail in terms of reproducibility, stability, and consistency in the half-life of the formulation. For this case study, the authors found that, for the operation on the microchip, the factors that most influence the quality of the microemulsion are the concentration of the oily phase, concentration of surfactant and substances flows; it was possible to study the effect of these factors on the droplet size through an experimental design. The results of the investigation showed that the batch process produces formulations with inconsistent oil phase drop sizes, while using the microdevice achieves a uniform dispersion of the oil phase due to the efficiency of the mixing process; a well mixing process in turn ensures that there is an adequate amount of surfactant on the surface of the droplets, thus preventing coalescence. Furthermore, the droplet sizes that are produced by microfluidic technology imply a greater permeation area of luliconazole through the skin. Some final comments made by Patil *et al.* [29] highlight the potential of microfluidics as a technology that offers feasibility for scaling microemulsion production processes and for accelerating screening of excipients in order to expedite the formulation of micro/nanoplatforms.

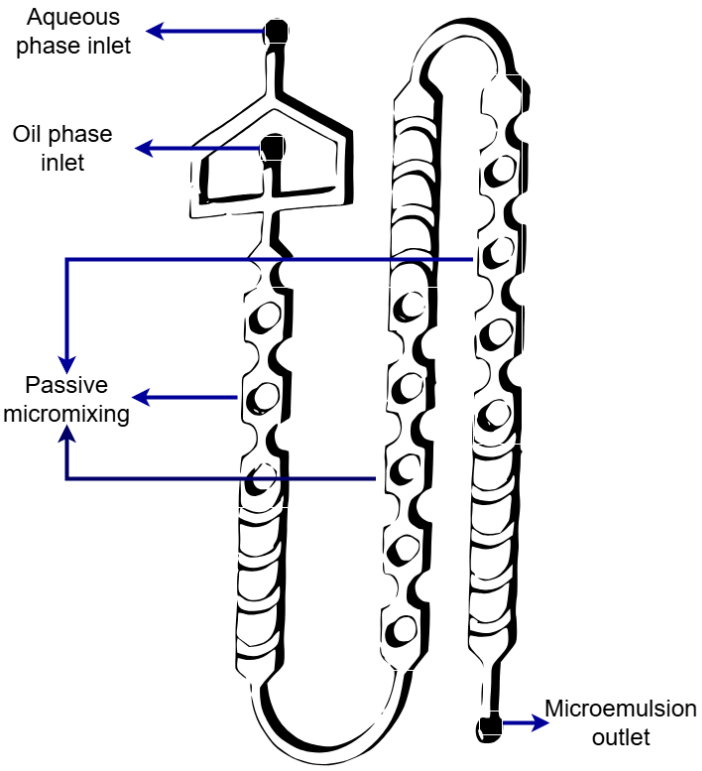

Figure 5. Schematic of the microchip used by Patil *et al.* [29].

Authors such as Mares *et al.* [30] confirm the usefulness of microfluidic science to control morphological aspects of pharmaceutical formulations. In this work, poly(lactic-co-glycolic) acid (PLGA) and polyethylene glycol (PEG)-based nanoparticles are produced using the manual mixing method and nanoprecipitation on a microchip method (the microdevice schematic is shown in Figure 6). First of all, it is worth mentioning that amphiphilic block copolymers such as PLGA have good biocompatibility and biodegradability, which makes them safe candidates for the formulation of systems aimed at treating conditions in humans [31]. PEG, for its part, works as a stabilizer and decreases the formation of the crown protein after the administration of the pharmaceutical form [32]. Conceptually, it should be considered that the formation of nanoparticles involves 3 stages which are nucleation, growth, and aggregation; if the mixing processes are inefficient, the nucleation process will be slow, and larger particles will be generated. On the other hand, if the mixing is too fast, the aggregation occurs in such a way that many nuclei will be formed. The microchip used in this study considers three input currents (two lateral and one central) whose arrangements and flows allow controlling the process of diffusion and formation of the nanoparticles. As results of this investigation, it was obtained that the particle sizes are dependent on the mixing of the solvent and antisolvent phase; the higher the antisolvent flow, the smaller the particle size. It is estimated that the particle sizes that can be produced by the nanoprecipitation method in the microdevice range from 44 nm to 97 nm depending on the solvent-antisolvent flow ratio and the size distribution obtained is narrow and unimodal. Moreover, with the manual mixing method, sizes ranging from 71 nm to 89 nm can be obtained depending on the proportions of solvent–antisolvent and it is expected sparse size distributions which tend to be bimodal. The intellectual product of this research allows us to affirm that by applying a nanoparticle production methodology based on microfluidic science, the final size of the particles can be controlled without having to alter the characteristics of the polymer, and consequently, the properties of the final product.

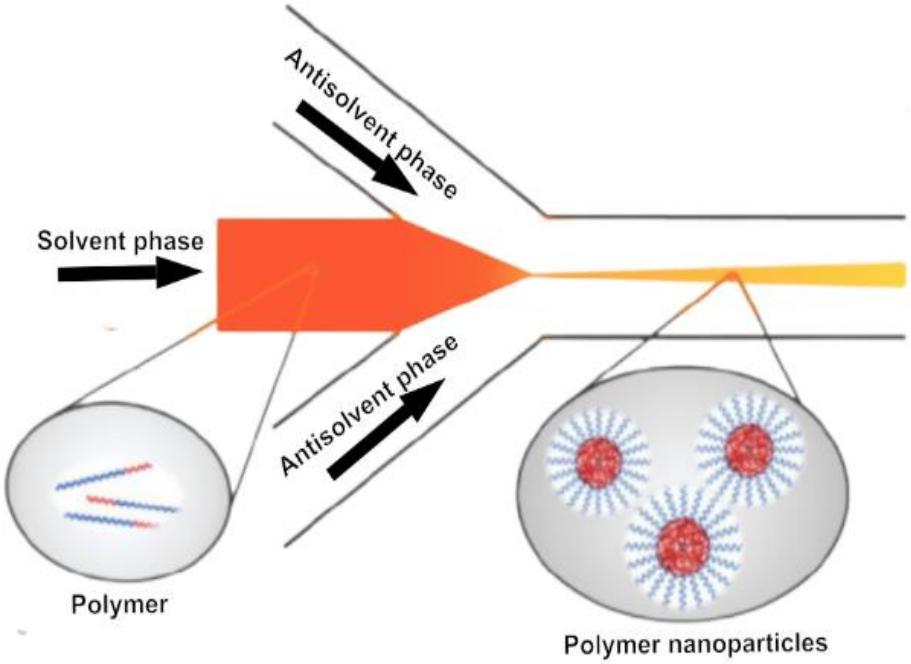

Figure 6. Diagram of the microchip used in the study by Mares *et al.* [30].

Other authors have explored slightly more precise methodologies for the control of final product quality characteristics, such is the case of Loy *et al.* [33]. In this research, the design of a modular platform for the operation of microfluidics is made. The first module is the control module or *Raspberry Pi module*, whose purpose is to execute scripts to control the pumps and the fraction collected in the second module, which corresponds to the *collection module*; the third module refers to the power supply of the microchip and is made up of the *programmable syringe pumps*; Finally, there is a *formulation module* (the scheme of the modular platform is shown in Figure 7). With this platform, polyplexes are formulated from siRNA (small interfering RNA) and oligomers; the electrostatic interaction between the cationic groups of polymers or oligomers with the negative charges of nucleic acids favor the formation of nanoparticles [34]. By using the previously described modular system, it was possible to obtain polyplexes with hydrodynamic diameters between 52.5 and 141 nm by modifying the oligomer/siRNA ratio, and polydispersity indices in the range of 0.03 and 0.114. The production platform proposed by Loy *et al.* [33] implies greater control and reproducibility of the formulations because each production cycle follows the same instructions provided by the software; In addition, this modular methodology can be useful for process scaling because, if necessary, the modules can be easily replaced by other more efficient components.

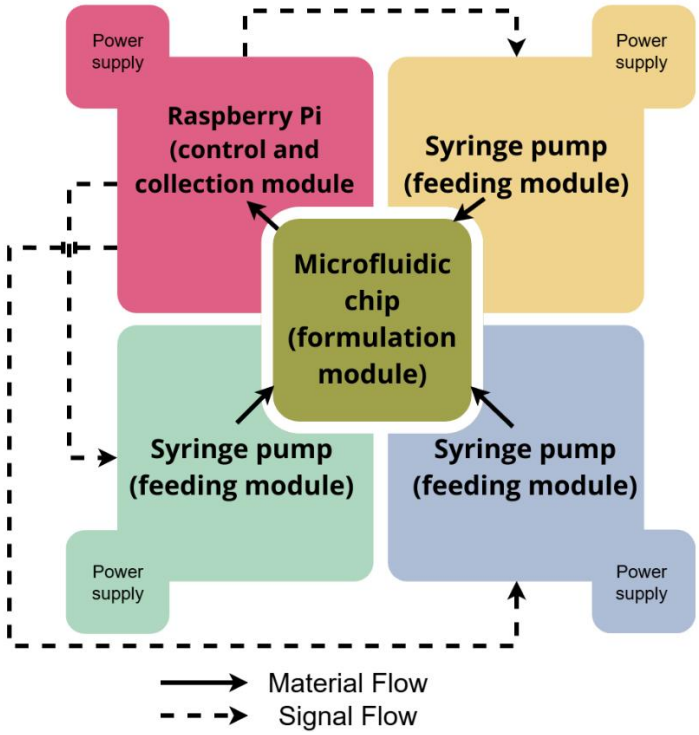

Figure 7. Diagram of the modular system used by Loy *et al.* [33].

In this research field on the automation of processes that can be carried out in microfluidic systems, there is also the study by Egorov *et al.* [35]. They discuss the integration of robotics and artificial intelligence (AI) in the synthesis of liposomes and polymeric drug delivery systems. According to the authors, due to the recent COVID-19 pandemic, the demand for robotic experimentation has increased; this has not only allowed samples to be analyzed safely but has also contributed to the minimization of human errors and fast formulations preparation. The use of these novel technologies is justified by the fact that in pharmaceutical forms manufacture, changes in process parameters and compositions can alter the properties of the final product, thus hindering the possibility of obtaining reproducible results [36, 37]. If areas of knowledge such as microfluidic science, robotics and machine learning are integrated into production processes, it is possible to increase understanding of structure-property relationships and interactions with tissues and cells. Despite the advantages of the approach explained above, there are challenges that must be addressed by the scientific community to get the most out of it, contribute to nanotechnology growth and pave paths to improve research in personalized medicine; among them are: "the limitation of data sets to report the results of machine learning and the change in the structure of chemical laboratories in order to open them up to students and experts from numerous fields of knowledge". A workflow scheme with the robotics – microfluidics – AI approach is shown in Figure 8:

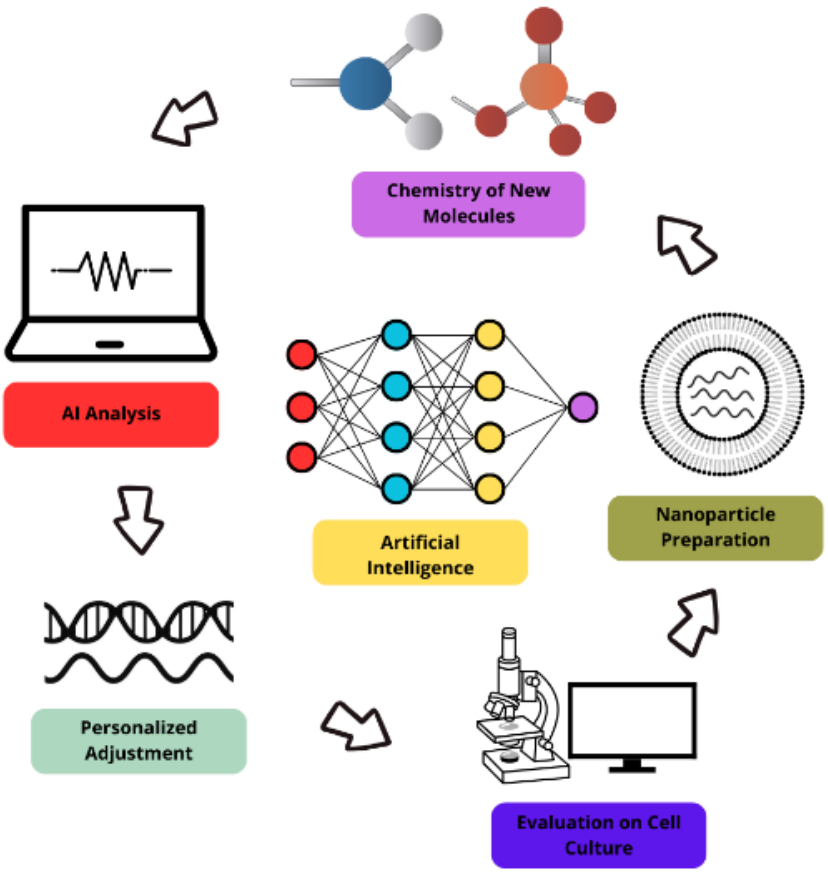

Figure 8. Workflow through the robotic approach - microfluidics - AI, proposed by Egorov *et al.* [35].

Microfluidics has been useful to produce controlled release systems for drugs and cosmetic active ingredients, because as previously mentioned, the advantages associated with this manufacturing method involve obtaining micro/nano platforms with precisely controlled properties and high reproducibility. This, added to an adequate selection of excipients, leads to obtaining formulations that respond to stimuli, which are profitable and/or that have good biocompatibility. These characteristics together make it feasible to apply different pharmaceutical forms (produced by microfluidic technology) in clinical trials [38]. To cite some examples, there is the study by Baby *et al.* [39] in which polymeric nanoparticles sensitive to pH are produced, loaded with curcumin, with potential application for the treatment of some types of cancer; This article has as particularities the spatial configuration of the microchip (it is in 3D and not in 2D, as usual, which contributes to a higher productivity and better control of the particle sizes) and that, depending on the operating conditions, it can be encapsulated different amounts of the active ingredient, managing to load up to 57% curcumin in the polymer system.

Lari *et al.* [40] for their part, carried out the production of nanoparticles of carboxymethyl chitosan crosslinked with $CaCl_2$ for the encapsulation of metformin hydrochloride in order to develop a treatment for type II diabetes. Thanks to the biocompatibility of the excipients used, the production method, and the release characteristics of the system, it was possible to demonstrate that the charged particles (synthesized by means of microfluidic technology) were more effective for the treatment of diabetes than metformin, conventionally administered.

Other excipients that are considered attractive for the development of controlled release systems, and that have been processed in microfluidic chips, are polylactic acid [41] and polysaccharides such as pullulan, mannan, hyaluronic acid, chitosan, alginate, dextran, among others. The latter are characterized by being biocompatible and biodegradable and, mainly, they are used for the production of nanogels that can encapsulate active principles by physical or chemical processes which can be carried out inside a microfluidic chip [42].

In the study made by Tiboni *et al.* [43], they propose the use of the 3D fused deposition methodology to economically produce a microchip whose purpose is to manipulate small volumes of raw materials to obtain polymeric nanoparticles and liposomes loaded with cannabidiol. In this research, the use of Computational Fluid Dynamics simulations allowed to evaluate the mixing potential of the microsystem proposed by the authors; this demonstrates the importance of supporting the methodological part of the investigations with simulations, since these facilitate optimizing designs and reducing experimentation times.

The integration of microfluidic technologies in the production of controlled release systems facilitates the systematic evaluation of various excipients and component mixtures that interact with the active ingredients of a formulation. This approach enables the rapid definition of design spaces by providing a clear understanding of how processing variables influence critical quality attributes. Moreover, process miniaturization allows for precise control over design parameters, ensuring the functional properties of the resulting pharmaceuticals or cosmetic products. Furthermore, the use of Design of Experiments (DoE) in building robust design spaces, as established by *Quality by Design* (QbD), has attracted significant interest in the development of commercially viable microfluidic systems. This bottom-up approach strengthens both product and process performance, paving the way for a successful scale-up phase aimed at large-scale manufacturing.

4. MICROFLUIDICS IN DRUG DISCOVERY

Microfluidic science has utility in any of the stages of new drug discovery and even in the development of pharmaceuticals; according to Kang *et al.* [44] these are: (1) target selection, (2) identification and optimization of the hit, (3) preclinical studies, (4) clinical trials, (5) manufacturing and (6) development of the final product. Some particular applications are based on high-throughput screening, toxicity assessments, and drug – cell cultures interaction studies [45-48]. There are a considerable number of microfluidic-based methodologies that seek to provide solutions to the drawbacks found in the conventional development cycle of a biologically active system. For example, when chemical synthesis is a critical step in obtaining new drugs, microscopic methods offer an advantage because heat and mass transfer is accelerated and, additionally, precise control can be achieved when dosing reagents; this translates into better yields and shorter residence times [49]. Studies such as the made by Torabinia *et al.* [49] have used the principle of dielectric wettability (which is based on the modification of the wettability of surfaces by applying electric fields) to carry out reaction, neutralization, evaporation and crystallization processes. Within the microdevice designed by the researchers there are reservoirs of the different solvents and reagents required for the reaction; In addition, there are sections of the chip where the transformation and separation stages are carried out. A schematic of the microsystem is shown in Figure 9. Another experimental activity developed in this study contemplates the optimization of the operating conditions and the voltages used for the manipulation of fluids. Once the working conditions in the microchip were optimized, yields ranging from 20.6% to 48.8% were obtained, depending on the initial concentration of

the reagent used in the study (benzoic acid). This research provides interesting bases for what could be the development of fully automated microplatforms.

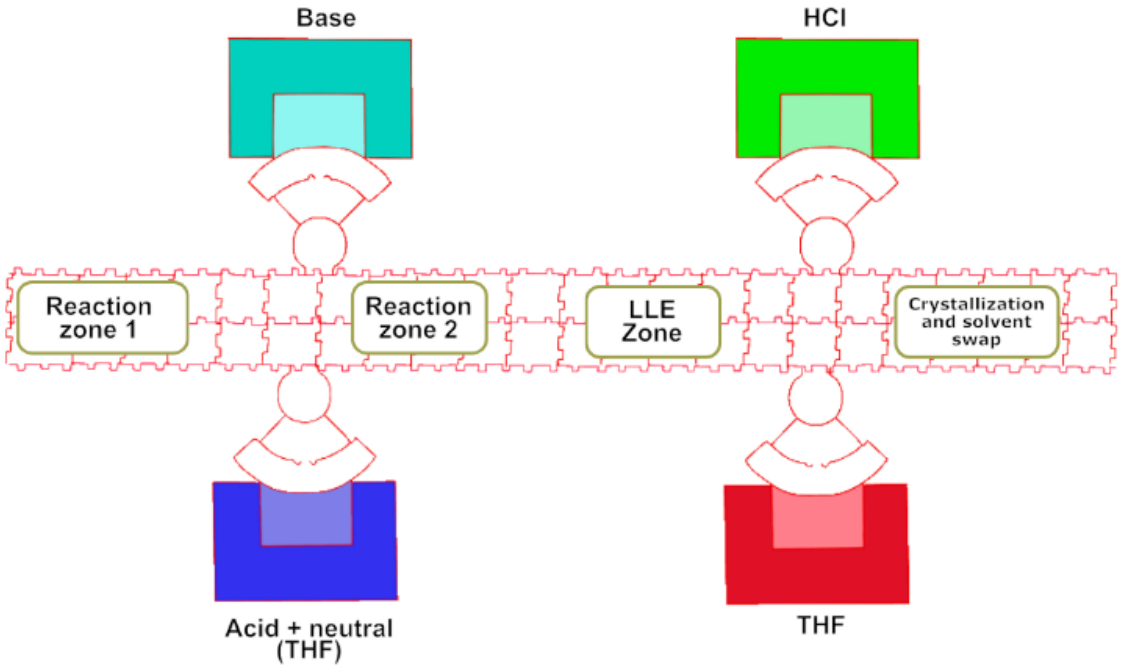

Figure 9. Scheme of the microchip for organic synthesis. Adapted from Torabinia *et al.* [49].

Within the area of high-resolution screening, microfluidic science has played a relevant role in recent years when it comes to searching for molecules with antifungal, antibiotic, and anti-cancer activity, mainly. Researchers such as Matilla [50] make clear the need to incorporate elements of microfluidic science in order to facilitate the search for molecules with antibiotic properties because miniaturization "facilitates the cultivation of microorganisms under a great variety of experimental conditions, the analysis of the microbial biodiversity of clinical and environmental samples, the screening of combinations of drugs to analyze their effectiveness against microorganisms resistant to multiple drugs, the analysis of interactions between biological molecules or the identification of enzymes with activities of interest".

High-resolution screening for drug discovery has been used in research such as the proposed by Oberpaul *et al.* [51]. Because the miniaturization of systems facilitates the manipulation of fluids, the study researchers were able to separate and cultivate strains of microorganisms extracted from soils by generating droplets on a microchip and using a methodology called FACS (Fluorescence-Activated Cell Sorting). Besides, these microfluidic elements were coupled with a methodology for the discovery of natural products guided by their bioactivity (bioguided fractionation using UHPLC-QTOF-MS in combination with molecular networking). This integration of tools for cell separation and evaluation of natural products allowed them to study the effect of more than 6,000 extracts against human pathogens and agricultural pests.

The discovery of drugs with anticancer activity has advanced considerably thanks to the implementation of three-dimensional cell cultures in microscopic systems. Conventional two-dimensional approaches can fail because they do not faithfully recreate the microenvironment with which cancer cells interact. According to Langhans [47], advances in three-dimensional cell culture have "provided opportunities to identify new targets and focus on microenvironmental factors that contribute to progression, drug response, and drug resistance". In this type of study, a wide variety of methodologies can be used to study the interactions of drugs with

the cells that are intended to be investigated; In essence, three-dimensional culture systems are carried out in three types of models (1) anchorage-dependent, (2) anchorage-independent and (3) hybrids of the two previous ones. One of the most widely used methodologies within the anchorage-dependent model is the cell growth in microfluidic devices. There is a wide variety of knowledge about three-dimensional cell culture and its correlation with microfluidics. In fact, Langhans states that this field of research has grown exponentially in the last 15 years. For this reason, it is recommended to refer to her review article for more details.

Nonetheless, the possibility of recreating physiological conditions with sufficient precision and detail by means of microfluidic devices has opened the doors to drug screening for the discovery of new therapies for already known diseases. Some examples are summarized below: in the article by Mistretta *et al.* [46], the potential of a microfluidic platform for the simultaneous experimental evaluation of multiple compounds on a study model was demonstrated. This model aimed to study the phenotypic change of single-cell, as reducing cell-to-cell variation can make bacterial populations vulnerable. Other articles have combined the development of organ-on-a-chip platforms with drug screening. These types of research are highly correlated because simulating realistic microenvironments makes it possible to understand mechanisms and accurately evaluate the effect of drugs on different conditions. For this reason, microsystems have been developed to facilitate drug discovery aimed at the treatment of cancer [52], neurodegenerative diseases [53], cardiovascular diseases [54], obesity [55], and even pain treatment through the understanding of neuronal signaling [56].

Microfluidic platforms have also had an important role in the discovery of drugs with antifungal activity. The search for molecules with these properties is of interest whether one takes into consideration that some types of infections caused by fungi can be fatal, there are few classes of compounds capable of treating this type of conditions, some drugs have considerable toxicity and even those can interact with other molecules of therapeutic action [57]. Microdevices have been used for high-resolution screening, particularly to observe the behavior of cells and biofilms cultured in hydrogels; this has provided relevant knowledge because according to Willaert [57] "a better understanding of fungal biofilms provides new opportunities for the development of agents and novel strategies that are urgently needed". Furthermore, microscopic systems have also been used to perform Antifungal Susceptibility Tests (AST) because this type of approximation is faster, more precise, and less costly; many of the studies carried out are based on the observation of cells (confined in volumes of the order of microns) by means of microscopy or fluorescence to obtain organisms resistance profiles; in this way it is possible to prescribe a patient with an effective drug [57].

Several studies focused on microfluidic systems in the pharmaceutical field—particularly for space applications—have integrated the *Quality by Design* (QbD) approach. These investigations address the functionality of cells and microorganisms under conditions of microgravity and space radiation, emphasizing the need for comprehensive knowledge generation and robust risk assessment. This is essential to ensure the reliable performance of microfluidic systems in environments with gravitational forces that differ from those on earth [58].

This module demonstrated the potential of applying microfluidic technologies to the evaluation of various active molecules, significantly reducing research and development times while fostering robust knowledge management. By assessing different drugs and their interactions with cultured human cells, it is possible to accurately determine the toxicity of pharmaceutical compounds, ensuring that active ingredient concentrations remain within safe thresholds. This contributes to the definition of safe design spaces for pharmaceutical products.

5. ORGAN-ON-A-CHIP TECHNOLOGY

Among the wide variety of biomedical methodologies for understanding, modeling, monitoring, and predicting drug responses, Organ-on-a-Chip (OoC) has shown potential since its conception in the early 21st century. OoC technology consists of a submillimeter *in vitro* platform designed to simulate specific functions of tissues or organs by cell cultures and microfluidics which allow to resemble real microenvironment conditions and biomechanical stimuli that surrounds the study system [59].

OoC platforms have attributes that make it stand out from other technologies. The most remarkable features are listed as: *i*) In the case of animal models, besides the ethical aspects, it has been demonstrated that they cannot equalize some human functions and responses due to differences in organs structure and cells complexity. These limitations imply, for example, lack of pathogenesis similarity compared to humans (which reduce their application in viral infections research) [60]; impossibility of using animal models in some neurodegenerative diseases researches owing to their less complex brain structure and cognitive functions [61]; and failure in resemble visual acuity due to lack of trichromacy [62]. All the challenges mentioned above have been addressed from the perspective of OoC technology. *ii*) Unlike classical two-dimensional cell cultures, OcC can simulate microenvironments and its alterations during disease, and has greater ability to assess drug responses in complex systems [63]. *iii*) It is estimated that OoC technology has an impact on different cost drivers in R&D process. A quantitative study made by Franzen *et al.* [64], showed that implementation of OoC could: reduce the cycle length in lead optimization stage, increase success rates at preclinical and phase II stages, and reduce considerably the cost at preclinical stage. The aforementioned is reflected numerically in an average reduction between 10% and 26% in R&D costs per new drug and savings of, approximately, 169 million USD to 706 million USD [64]. *iv*) Facilitate high-throughput screening of large drug libraries and its effect on different types of human cells; this could pave the way to personalized prescriptions by understanding the physiological characteristics of each patient. *v*) Represents a potential tool for nanomedicine assessment [65], pharmacokinetics and pharmacodynamics studies, and continuous dynamic monitoring in disease modeling [59]. *vi*) It has demonstrated potential to replicate *in vivo* responses and therefore clinical trials and toxicity studies could be facilitated [66].

The different approaches made through OoC seek to establish simplistic models that provide information about mechanistic aspects of diseases and drug-cells interactions, mainly. For that reason, it is critical to understand the anatomy of the organ to study which involves microstructures, cellular microenvironments and mechanical forces implicated; some key factors are listed as: *i*) In lung-on-a-Chip applications it must be considered air-blood microenvironment as well as mechanical stretching and specific cell types [66]. *ii*) In gut-on-a-Chip studies it is important to mimic peristalsis and the microbial environment [66]. *iii*) Retina-on-a-Chip models face challenges due to the complex 3D physiological structure; for that reason it is necessary to evaluate cells characteristics and microphysiology associated to the process of interest [62]. *iv*) In cardiovascular models such as blood-vessel-on-chip and heart-on-chip it is recommended to consider shear stresses, tensile strains, flow type, and mechanical and electrical stimulation since it determines cell morphologies, proliferation and even it is critical in evaluating drug cardiotoxicity [66]. *v*) In kidney models a key concept is related to the constant flow of the glomerular filtrate because it implies continuous shear rates which have an effect on epithelial cells morphology [66]. *vi*) In Organ-on-a-Chip models for female reproductive

systems, researchers have explored elements such as placental barriers, cellular constituents, structural organization and biomechanical microenvironment like blood flow [67, 68].

Without a doubt, the OoC field is significantly vast and for each tissue or organ model, researchers must evaluate and discern among the plethora of micro-conditions that can affect the performance and the ability to predict biological behaviors in the human being. However, a systematic approach for constructing organs-on-a-chip and for analyzing microscopic phenomena has established a tool with the potential to replace conventional methodologies for diseases, and drug interactions assessment.

An example of the stated above is found in the paper by Achberger *et al.* [62]; here it is exposed the importance of OoC technology to simulate the complex stratified retinal tissue. By means of conventional models for drug development and diseases research it is not possible to, simultaneously, recreate crucial elements such as physiological structures, perfusion, constant nutrients supply, biological barriers functions, cell interactions, and mechanical stability. The authors developed a microfluidic platform able to mimic the human retina anatomy *in vitro;* to perform this task, inside the chip top layer was cultured retinal organoids derived from induced pluripotent stem cells (hiPSC), whereas the bottom layer had the function of supplying nutrients, resembling a vasculature perfusion. The retina-on-a-chip model proposed by Achberger *et al*. was tested to study the secretion kinetics and the controlled delivery of compounds to the tissue, the establishment of interactions between segment structures of the retinal organoid and retinal pigment epithelium cells. Moreover, it was possible to assess the retinal functions by evaluating the ability to produce an *in vivo*-like calcium flux and the functionality of the visual cycle was verified.

Once the platform's ability to recreate physiological functions was verified, its potential to carry out drug development and toxicity studies was evaluated by exposing the system to chloroquine and gentamicin. After drug exposure it was quantified the cell viability though a staining method; the results suggest that concentrations above 80 μg/mL of chloroquine and 0.5 mg/mL of gentamicin had an important effect on cell death, which was an expected behavior because there are reports in the literature that confirm the pathological side effects of these drugs on the retina.

In the same way, it is found a wide variety of research from 2019 to 2025 that study the mechanistic of diseases to identify determining physiological aspects that can be the starting point for the development of helpful treatments. As examples, there are investigations dedicated to study the effect of ambient fine particles on carcinogenic development [69], prediabetic hyperglycemia [70], polycystic kidney disease mechanisms [71], human cardiac development [72] (among a quantity of more than 2500 documents according to Scopus database in the aforementioned data range).

This type of approach, which seeks to understand diseases in depth to find effective and personalized therapies, is a key pivot for the development of drugs based on QbD because they provide a comprehensive view of the patient's response in terms of toxicity, effectiveness, and safety, the latter are essential for the rational application of the methodology and, in combination with the nanomedicine, it is possible to have a parametric control from the manufacture of the formulation to the functionality and biological activity *in vivo*.

Since there are a plethora of papers that can be classified into the "organ-on-a-chip technology" group, it is recommended to delve into specialized review articles on specific topics; if the expectation is to deepen on the importance of OoC mechanical stimuli in diseases assessment see [66]; to explore the usefulness of OoC for nanomedicine evaluation refer to [65], to consult some innovations in disease modeling and drug development in OoC please read [59]. Also, there is almost one review article per organ or tissue in the human body that represents

a challenge from the biological, pharmacological, pharmacodynamic and pharmacokinetic point of view. In fact, of the 5,088 articles published in Scopus between 2019 and 2025 related to OoC technology, almost a third (31%) are review articles.

This group of microfluidic applications is of great interest during the development stages of pharmaceuticals and even cosmetic products, as it enables the cultivation of cells from the patient—or the target individual for a therapy or treatment—on microchips [73]. This approach makes it possible to understand the mechanistic behavior of their cellular response and to design formulations tailored to their specific needs. Understanding microscale interactions is essential to effectively leverage critical process variables, design parameters, and quality attributes within a defined design space, with the goal of developing safe and effective products.

6. PERSPECTIVES

To date, and to the best of our knowledge, the scientific investigations that bring together microfluidic and pharmaceutical sciences have focused on the different stages of medicine design from an isolated perspective and focusing on the elucidation of fundamentals. However, as has been mentioned throughout this article, microfluidic science has applications in each of the phases of product development, therefore, it is expected that in future research it will be possible to have platforms that carry out all design activities in a single platform, namely: producing nanomedicines, characterizing critical parameters in functional performance, and evaluating its toxicity, therapeutic activity and security in order to replace the models that nowadays are considered conventional. Likewise, research that quantitatively demonstrates the advantages of microfluidics over other technologies will be relevant to attract more researchers to the pharmaceutical area and even to cosmetic and phytotherapeutic sectors. Furthermore, with the accelerated development of artificial intelligence, it is likely that the application of such computational tools in the development of microplatforms will become more popular, enabling them to perform many more tasks in a more intuitive and efficient manner.

7. CONCLUSIONS

Microfluidic systems serve as a powerful tool for the entire lifecycle of pharmaceutical products development and enhance the knowledge basis for the effective application of quality-based methodologies. This technology can be used to improve each of the key items that are highlighted in the ICH guidelines since its bottom-up approach allows a precise parametric control and therefore, it is possible to establish effects and correlations between microscopic events, product quality attributes, functionalities, and process variables. Moreover, the latent opportunity to evaluate medicines, drugs and therapies in human cells makes it an ethical and profitable alternative to predict the response of people in the clinical phases.

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AUTHOR CONTRIBUTIONS

Edward Rodriguez led the manuscript writing, conducted the background research, performed the information analysis, and made the necessary adjustments. Helber Barbosa contributed to the supervision of the work and provided critical feedback on the manuscript. Bibiana Vallejo contributed by providing relevant information, supervising the research, reviewing the manuscript, and offering feedback.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this article.

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