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A Critical Review on Microfluidics in Drug Screening

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Abstract

This literature review is a critical review on microfluidics in drug screening. It consists of an introduction, contemporary technologies used, future prospects and trends, and what to look for moving forward.

Introduction:

Conventional drug screening relies heavily on animal models and cell cultures. The ability of these traditional technologies to predict human response and produce reliable and actionable data is severely limited. The methods produce inaccurate and insufficient data because they do not understand the complex intricacies of the human reaction to medications and drugs. These limitations have led to a need for more dependable and effective drug screening technology.

The field of microfluidics, which studies the manipulation of fluids in microchannels, has drawn attention for its potential to address the drawbacks of traditional techniques [1]. Microfluidic systems enable control of experimental conditions, lowering reagent consumption, and allowing high-throughput screening (HTS) in a significantly shortened amount of time compared to traditional methods by using microscale biological and chemical assays. Furthermore, by utilizing a combination of organ-on-a-chip (OOC) systems, dynamic fluid flow, and three-dimensional cell cultures, microfluidic devices can closely replicate physiological settings and provide more predictive models for human drug responses and data collection [2].

Microfluidics is more flexible than only processing small quantities and running parallelized experiments. The microvasculature of the human circulatory system and the complicated cellular architecture of organs are only two examples of the complex biological settings that microfluidic technologies can mimic and process. This complex ability lessens the reliance on traditional methods of animal models and improves the validity and accuracy of preclinical testing by allowing researchers another avenue to examine pharmacological effects in more relevant settings. In addition, by enabling the screening of medications on patient specific cells or tissues, microfluidic technologies open up a significant avenue of possibility to fully transform personalized medicine and allow for customized therapy.

In recent years, microfluidic technologies and devices have been utilized increasingly in drug screening for many applications. Some of these applications are toxicity level assessments, lead detection, and drug discovery processing and delivery. As the pharmaceutical industry continues to implement microfluidic technologies into their works, it is crucial to evaluate and process the state of microfluidics today, the benefits and drawbacks of using microfluidics, and potential future avenues of possibility for microfluidic technology in the pharmaceutical industry as it continues to be adopted.

Contemporary Microfluidic Technologies in Drug Screening, Discovery and Processing:

The implementation of microfluidic technologies has revolutionized the drug screening field through automation of traditional laboratory procedures. The technologies allow for fluid manipulation in microchannels through precise control over chemical and biological responses in drug testing. Additionally, the utilization of Droplet Microfluidics systems, Organ-on-a-Chip (OOC), and Lab-on-a-Chip (LOC) are three major developments that will contribute significantly to drug screening capabilities [3]. Each of the systems provides its own unique capabilities and has already contributed extensively to a more reliable and accurate drug discovery, processing, and production procedure.

Lab-on-a-Chip (LOC) Devices -

The Lab-on-a-Chip (LOC) is a type of microfluidic technology that combines multiple laboratory procedures onto a single chip that is within the range of a few centimeters to a few millimeters in area [4]. Additionally, LOC devices can perform intricate chemical, biological, and physical processes with the use of very few reagents. This low usage of reagents and cost bolsters LOC into the spotlight of being a valuable microfluidic device in drug screening.

A main area of LOC technology is in cell-based assays. These improvements in technology allow microchannel growth of culture cells and the exposure of those cells to numerous drug compounds for testing and data collection. The sensitivity and real-time monitoring of drug responses are progressed through the usage of the miniature-sized channels and precise LOC technology. Furthermore, high-throughput screening (HTS) tests have been used on a smaller scale by LOC devices, significantly reducing the costs and amount of time needed for drug discovery [5]. An example of this instance is when LOC technology was used as a multiplexed screener of small molecule libraries to detect inhibitors for infectious diseases and cancer.

LOC technology allows for the combination of several analytical techniques on one platform, such as fluorescence, electrochemical detection, and mass spectrometry. This complex and interconnected integration improves the efficiency of the throughput and enables greater versatility of drug screening capabilities.

Organ-on-a-Chip (OOC) Technologies -

The Organ-on-a-Chip (OOC) device mimics physiological functions of human organs on micro-engineered chips. These micro-engineered chips typically consist of living cells made up of multiple microfluidic channels [6]. Additionally, they imitate the functionality of organs, such as the heart and brain. The introduction of OOC technology into the microfluidic space has opened up a potential alternative to traditional measures of in vitro experimental assays and animal models [7]. This provides more conventional and accurate means of understanding human responses to drugs.

An example of these technologies is its implementation in liver functionality and testing. Liver-on-a-chip technology has been produced to target data collection on drug metabolism and hepatotoxicity [8]. The technology implements a microenvironment that corresponds identically to a human liver's function, including nutrition and oxygen flow. This allows for a deepened assessment of drug-induced liver damage [9]. Similarly, cardiotoxicity is a common adverse effect of drug intake of several medications that can be studied through the use of heart-on-a-chip devices. The heart-on-a-chip device provides a model for interpreting data collection of screening of medications that display adverse effects on human cardiovascular health.

OOC technology has gained increasing integration into multi-organ-on-a-chip systems, which model the

interactions of various organs to understand drug processing [10]. This integration has been fundamental in the holistic research of drug absorption, distribution, metabolism, and excretion (ADME). Through the utilization of all these different OOC technologies, there has been a more comprehensive and reliable collection of data to understand drug effects of several medications in the body.

Centrifugal Microfluidics -

Lab-on-a-disc technologies, commonly known as centrifugal microfluidics, manipulate centrifugal force to control fluids within a rotating disc-shaped device. This methodology has fielded multiple advantages for drug screening capabilities, including the ability to perform simultaneous tests on a single apparatus [11]. Additionally, it allows for the processing of multiple steps such as sample mixing, preparation, and analysis.

The primary application for centrifugal microfluidic devices is its effective compatibility for high-throughput screening testing because they can properly analyze and process multiple samples at once. Furthermore, the effects of the drugs in real time in the human body can be tracked. The tracking is accomplished in combination with optical detection methods such as fluorescence or absorbance-based assays. Centrifugal microfluidics have been a staple application procedure incorporated into the field due to its inexpensive costs, simplicity of use, and accessibility. The implementation of automated sample processing and handling has reduced the requirement for manual intervention.

Technology	Key Features	Applications
Lab-on-a-Chip (LOC)	Reduced reagent use, inexpensive cost, HTS usage, and real-time monitoring	Complex cell-based assays, HTS of pharmaceutical drug compounds, fluorescence detection, and multiplexed screening
Organ-on-a-Chip (OOC)	Imitation of human physiological responses of organs and various organ-on-a-cip models for ADME	Drug metabolism, organ imitation and functioning data collection, and ADME applications
Centrifugal Microfluidics	Centrifugal force application for fluid control, simultaneous sample processing, inexpensive cost, and simplicit use	Real-time adverse drug effect monitoring, HTS applications, and automated sample processing

High-Throughput Drug Screening (HTS) Applications:

High-Throughput Screening (HTS) is a fundamental application that is involved in drug discovery. It enhances the ability to evaluate chemical libraries and identify potential drug compounds that can be suitable candidates for pharmaceutical use [12]. Microfluidic advancements have significantly contributed to the applications of HTS in drug discovery. In addition, they have markedly reduced the screening procedure, time, and costs and have played a pivotal role in improving the effectiveness of drug development and data collection.

Bead-Based Microfluidic Screening (BBMS) -

Bead-Based Microfluidic Screening (BBMS) is an innovative screening measure that uses biological applications to effectively screen drugs. In BBMS, the tool involves the use of laboratory produced microscopic beads that are coated with target molecules. These target molecules can include antibodies, enzymes, and DNA [13]. The functionality of the target molecules are to be involved in a passageway through the microfluidic channels to potential drug compounds. BBMS allows for processes to be conducted in a highly regulated manner and be reproduced numerous times due to the possibility of bead reusage.

The advantages fielded by BBMS for HTS are multiplex assays, allowing for multiple targets to be screened simultaneously similarly to centrifugal microfluidic devices. This has proven to be extremely useful for researchers when targeting potential drug candidates to filter out outlier drug candidates. Additionally, BBMS has displayed efficacy in being an appropriate diagnostic tool for identification of specific disease biomarkers. BBMS' multi-usage has fielded it as an excellent innovation that has shown promise in both scientific and clinical research settings.

Microarray-Based Microfluidic Technology (MBM) -

Microarray-Based Microfluidic (MBM) devices have played a fundamental role in HTS. The device enables hundreds of compounds to be tested simultaneously [14]. This significantly increases the screening throughput. Similarly to BBMS, MBM's can use target molecules on a microarray to expose and identify potential pharmaceutical drug candidates.

Microarray and microfluidic technology combine to enhance accuracy of the reagent and sample delivery to targeted arrays. This technology allows for a significant reduction in reagent use and costs, increasing the potential for more drug screening tests. Similarly to centrifugal microfluidics, microarrays can work in conjunction with detection technologies to process real-time drug interaction monitoring based on fluorescence and mass spectrometry.

Future Trends and Directions:

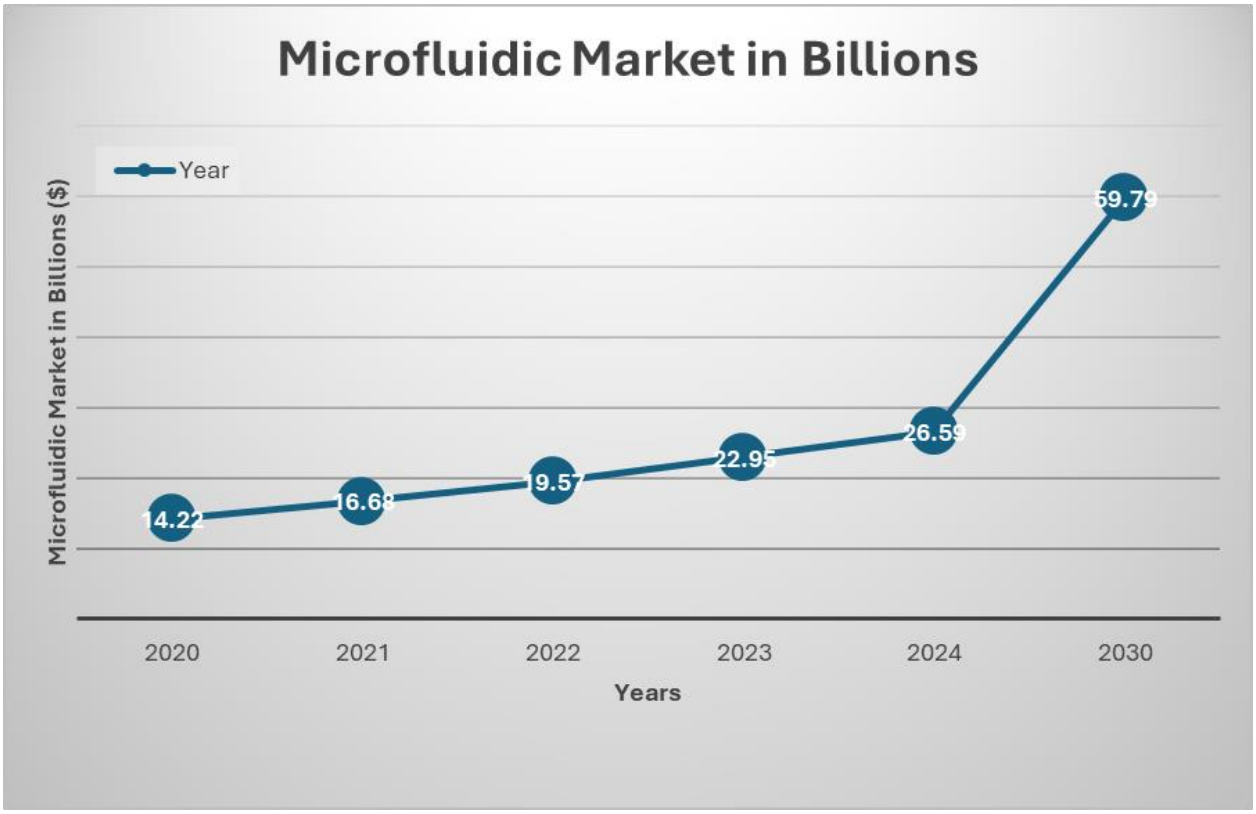
Microfluidics in Customized Medicinal Care -

With the rise of global attention towards personalized medicinal care, microfluidic technologies can play a fundamental role in making this a possibility. Microfluidics offer drug screening capabilities on patient-specific cells, allowing scientists to offer customary care through specific identification of an individual's condition [15]. Microfluidics thrive in this aspect as they can accurately and reliably handle small sample volumes and conduct high-throughput screening [16].

Patient-specific cells can be used to screen for potential pharmaceutical compounds that can be effective for a personalized individual. An example of this is in cystic fibrosis, where different mutations of the CFTR gene can vary the treatment plans recommended. The ability for personalization allows treatment plans to be more targeted and effective, enhancing patient recovery [17]. The future trend of microfluidics in conjunction with genomic and protein data shows promising possibilities for customary medicinal care. Also, microfluidics have shown promising avenues of predicting patient reactions to treatments by collecting data from their genomic composition, protein expression, and prior biological and physiological responses [18].

Conjunction with CRISPR and Gene Editing Tools -

CRISPR-Cas9 and gene editing tools show promising possibilities in conjunction with microfluidic technologies. Microfluidic technology can be used with high-throughput CRISPR tools to find potential drug compounds or evaluate and collect data on drug resistance processes [19]. Additionally, the combination of both tools has created opportunities for analyzing complex disease models and creating patient-specific models. The patient-specific models can address specific complex diseases through evaluation of genetic and environmental factors that can aid in disease eradication. The tools have paved the way for possibilities for using high-throughput screening to assess effective gene treatments and search for optimal drug products. This creates an opportunity for the discovery and implementation of new pharmaceutical methodologies and compounds that can aid in personalized medicinal care and patient disease treatment.



The chart above displays cash flow into the microfluidic market in billions, showing projections of an increase in cash flow by the year 2030. This chart suggests the increase in avenues of opportunities that microfluidic technology will have in the medical field with an increase in investment each year.

Conclusion:

Microfluidic technology has played a fundamental role in drug screening evolution and continues to offer increased levels of effectiveness, accuracy, and usage in drug and pharmaceutical compound discovery. Microfluidic devices are able to tackle the drawbacks and disadvantages posed by conventional methods such as cost, equipment use, and time. This allows researchers and scientists to utilize microfluidics effectively in research and clinical settings. The advantages posed by microfluidics include the ability to use minor-scale testing, cost savings, enhanced HTS, ability to mimic physiological conditions, and ability to real-time monitor drug and compound effects and collect data [20]. All these advantages pave the

avenue of opportunities for microfluidics to become a staple technological advancements that will be a hallmark in the drug screening, identification, and production process.

The increasing investment and development of microfluidic technology shows promising signs of its permanent introduction into drug screening and discovery. The capabilities of microfluidics to mimic in vivo conditions, such as fluid dynamics and organ function, shows promise in the ability to detect potential drugs and testing. This can ultimately create a route for customized clinical care and improve the efficacy of treatment plans. The future for microfluidic technologies is very bright, as microfluidics has the potential to be at the forefront of drug discovery to treat diseases, address alarming increases in chronic illnesses, and provide personalized medical care to individuals for optimal disease eradication.

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