Microfluidics Relevant Approaches in Drug Delivery System Treatment of Cancer – A Review

Mekha Kunjumon*, Libina Babu and Aswathy Boss
Nazareth College of Pharmacy,Othera p.o ,Thiruvalla ,India

ABSTRACT

Microfluidics technology is a promising method for creating advanced drug delivery systems, particularly in cancer detection and treatment. These systems provide accurate, efficient, and user-friendly methods for cancer detection and treatment by examining small samples. Microfluidic devices can produce nanoparticles for medication administration and identify cancer-diagnostic variables from biological fluids. Due to their high sensitivity, high throughput, and low cost, microfluidics may be useful in cancer study. While not currently used in clinical settings, microfluidic systems are expected to replace current technologies as the primary means of cancer diagnosis and treatment. Microfluidic lab-on-a-chip platforms have shown potential in designing novel procedures for cancer detection, therapy, and disease follow-up, as well as developing new drug delivery systems for cancer treatment. They are also being considered a rising method in natural disease studies due to their small volume and ability to be used in clinical settings.[1,2.3]

Keywords: Microfluidics, detection, treatment

1. INTRODUCTION

Cancer is the second leading cause of death worldwide, with malignant growth being the most prevalent type. In the US, around 1.6 million cases of malignant growth were reported in 2016, with 500,000 disease-related deaths recorded. Over 15 million US individuals have malignant growth, with the number expected to increase to 19 million by 2024, causing a significant financial burden of over 130 billion dollars annually. To improve prognosis, improve life quality, reduce medical costs, and increase recovery chances in cancer patients, more advanced technologies are needed to detect cancers.

Technologies like positron emission tomography, diagnostic magnetic resonance imaging, and computed tomography are used to plan cancer treatment, but they face challenges, high costs, and limited availability. Microfluidic frameworks, which are designed liquid streams restricted to small items, have become significant models in cancer-related studies. They have become significant models in disease exploration, finding, and testing.

Microfluidic technology allows for controlling liquid on a micron-scale from 1 to 1,000 µm, making it a powerful tool for performing complex laboratory procedures on microchips. Its high limit, efficient components, and accuracy make it a highly productive stage for diagnosing. Microfluidics can also be used to develop unique division techniques, such as laminar flow, supporting auxiliary powers, and designing calculations to explore, limit, and gather cells and cell-specific items[5,6,7,8]

2. MICROFLUIDIC FABRICATION TECHNIQUES

Various techniques are proposed for manufacturing microfluidic gadgets, but these have not been adjusted for organic purposes. Focus should be on minimal cost, simple activity, low waste, and high creation, with appropriate creation techniques and professionals discussed

2.1. Chemical processes

Electrochemical discharge machining, wet etching, and dry etching are chemical processes used for non-conducting materials like ceramics and glass. Wet etching has fast etching speed and simultaneous processing, but has safety and environmental risks. Dry etching overcomes these limitations but is less preferred due to its low speed.

2.2. Mechanical processes

Despite mechanical technique limitations (reduced accuracy and efficiency compared to lithographic methods), they are used to design and fabricate microfluidic systems based on silicon, glass, polymers, micro and nanoimprinting, and hot embossing[11]. Also, mechanical cutting techniques, abrasive jet machining, and ultrasonic machining are used to construct complex three-dimensional structures due to their low cost [11].

2.3 Laser-based processes

Laser plotting and cutting is a quick and easy fabrication method for rapid prototyping, using laser pillars to etch desired designs onto substrates like PMMA, polycarbonate, and PDMS. However, controlling cross-segment applications can be complex.

2.4. Three-dimensional printing

3D printing is one of the most powerful and well-liked methods for making microfluidic systems. It has unique advantages over other methods, including design flexibility, reusability, high resolution, and ease of manufacturing [12]. Polyjet printing, inkjet printing, liquid silt demonstrating, and stereo lithography are among the different techniques utilized for 3D printing and electrospinning [12].

2.5. Hybrid technologies

Hybrid technologies are a novel approach created to overcome the challenges and limitations posed by each method. It is difficult to design transparent microfluidic devices using one of the hybrid systems,

which is a combined 3D system based on laser laminated printing and micromachine. Another half breed innovation that coordinates the upsides of xerography and warm cover in the printing system was a three-layered model, which empowered fast creation with high potential in development [11].

Microfluidic devices have been used to create self-assembling gene and drug delivery systems at Nano and micro-sizes. These systems use multiple reagent streams and interfacial layers to create carriers. Most PDMS microfluidic chips
have rectangular molded channels, allowing for the hydrodynamic diameter [D_h] idea. The calculation of D_h also helps to estimate the flow through irregular channel shapes such as channels with a circular cross-section

$$D_h = 4 \times A \div P_{wet}$$

where A is the cross-section area of flow-through and P_{wet} is the wetted perimeter. The calculation of Dh helps estimate the flow through irregular channel shapes, such as channels with a circular cross-section. Platforms for preparing self-assembled particulate drug delivery systems include hydrodynamic flow focusing (HFF), microfluidic mixer in conjunction with staggered Herringbone micromixer (SHM), or microfluidic mixer in conjunction with SHM. Self-assembled carriers are generated through HFF by controlling mixing rates between fluid streams based on microchannel shapes, flow rates, and diffusion coefficients of different miscible streams. Setting the flow rate ratios (FRR) of water and a solvent containing polymers of lipids precisely enhances the self-assembly reaction and controls the degree of mixing within the microfluidic channel. The HFF method usually produces self-assembled drug delivery systems smaller than 1 μm, allowing better delivery across physiological barriers. Microfluidic systems offer multilayer carriers for delivering multiple factors, but cannot incorporate amphiphilic drugs, requiring chemical modification before manufacturing.[18]

3. DROPLET BASED CARRIER

Droplet-based microfluidics is a widely used method for synthesizing nano- and micro-particles for biomolecule encapsulation and analysis. Strategies include hydrodynamics, pneumatic pressure, optical techniques, and electrical techniques. T-junction devices create emulsions by adding surfactants and aqueous or oil phase. The flow pattern can be planar or cylindrical, and droplet size, velocity, and frequency can be controlled. Co-flowing devices like microfluidic devices involve dripping and jetting, influenced by fluid velocities, surface tension, viscosities, densities, and channel geometries, where droplets break a thin stream.

3.1 Non-Spherical Drug Delivery Systems

Microfluidic techniques can create non-spherical particles for drug delivery, mimicking biological cell properties. These particles are crucial for invivo biodistribution, circulation time, and cellular uptake, with anisotropic nanoparticles enhancing gene silencing efficiency.[20,22]

3.2 Nucleic Acid Delivery Systems

Microfluidic techniques have been used for gene carrier fabrication and DNA synthesis using cationic polymers and lipids. These carriers, such as polyethyleneimine-plasmid DNA Nano-carriers, enhance cell viability and gene transfer efficiency, and have potential for gene delivery and vaccine therapy.

4. MICROFLUIDIC TOOL FOR CANCER DIAGNOSIS

Microfluidic frameworks offer significant opportunities for sensor devices in clinical diagnosis, natural identification, and climate or wastewater monitoring.

They have been used in malignant growth research for the past decade, providing precise disease biomarkers. Recent advancements in microfluidic sensor frameworks and their use in cancer research, diagnosis, and treatment are examined.[31-35]

Nguyen et al. developed an electrical cell-impedance detecting system that combined with microfluidic chips to detect single cancer cell movement in three-dimensional networks. This method effectively captured cancer cells sequentially without physical contact. Shah et al. developed a biopolymer framework for cell recovery from microfluidic devices, using a hydrogel covering for better performance in various physiological solutions. They used this framework for the capture and delivery of epithelial cell adhesion particles (EpCAM) communicating malignant growth cells, demonstrating no significant impact on proliferative potential and cell viability. (Figure 1c) [36].

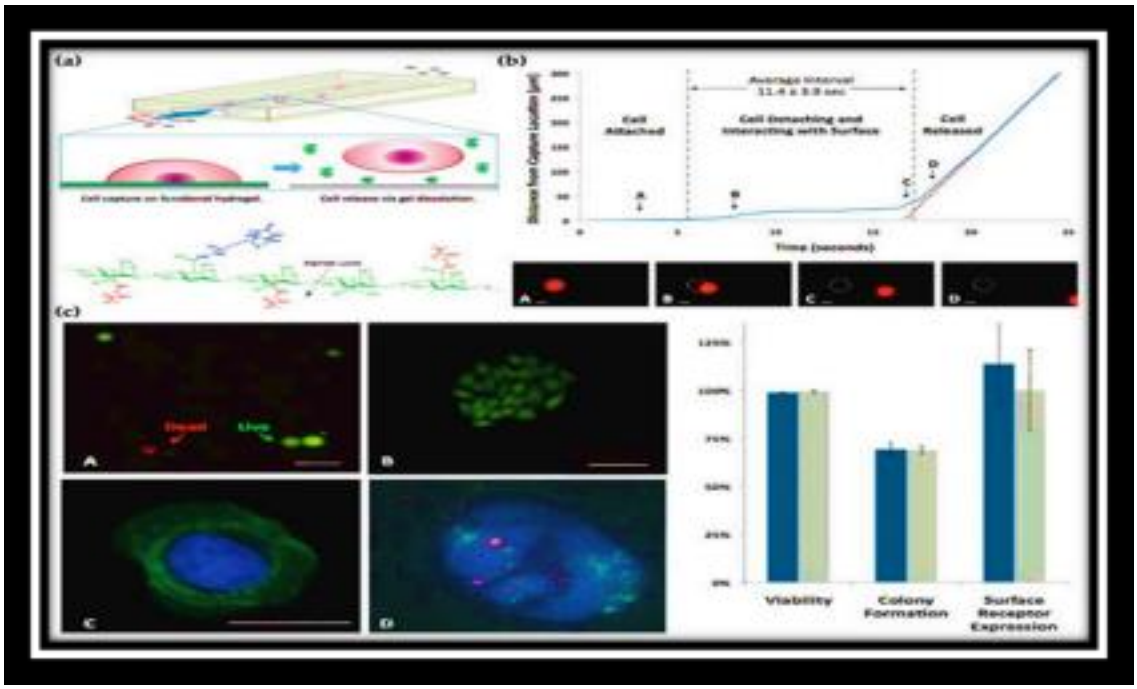

Figure 1. (a) Sacrificial hydrogel coatings microfluidic devices; (b) The gentle nature of the release process as the cell starts; (c) released cells for (A) viability using a fluorescent LIVE (green)/DEAD (red) assay and (B) colony formation, (C) immunostaining of cell surface receptors, (D) FISH (fluorescence in situ hybridization) analysis in a released HER2 (green probe) amplified breast cancer cell; the control probe.

The study by Zhao et al. used microfluidic systems to study 3-D metastasis in tumor and stromal cell spheroids merging and pairing. The device showed one-to-one pairing tumor-fibroblast spheroid, providing an efficient method to simulate tumor microenvironment in vivo. The study demonstrated the generation of tumor cell aggregates within 24 hours for the first and second chips.[32]

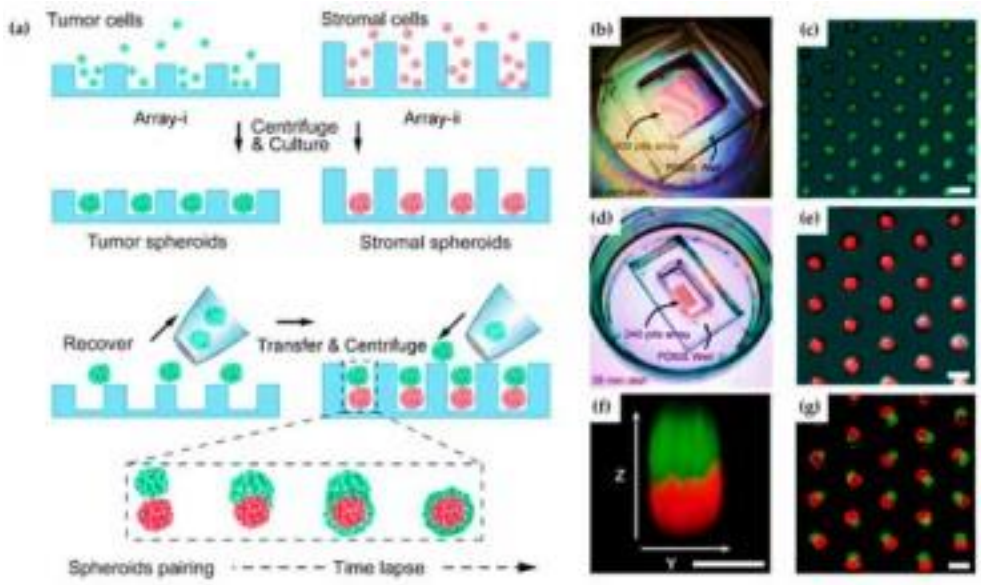

Figure 2. (a) The microfluidic micro well array-based spheroids pairing; (b–e) representative pictures of chips; (f) tumor−stroma pairing with green and red fluorescence; and, (g) image of heterotypic cell spheroid pairs [34].

Chu et al. developed a nanomaterial-based microfluidic chip for ultra-sensitive detection of microRNA (miRNA) at attomole levels for cancer diagnosis. The chip, based on microfluidic technology, showed a linear range detection between 1.0 aM and 10 nM and a 0.146 aM limit of detection value without amplification in 35 minutes using 2.0 μL sample volume. The study demonstrated the chip's great capacity for early cancer detection, with samples from healthy humans and breast cancer patients. The chip was assembled with graphene oxide as a novel nanomaterial.[34]

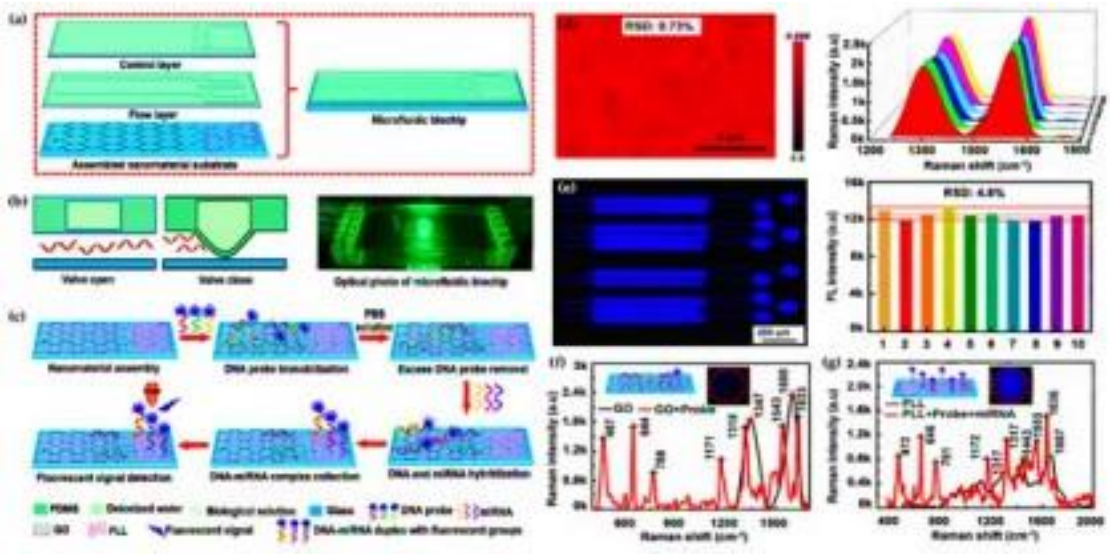

Figure 3. İllustration of the microfluidic chip; and the Raman mapping and representative (a–c) was also used to indicate all areas of interest and were assembled with graphene oxide (GO). (d–g) shows the fluorescence mapping images of the detection chamber [42].

Otieno et al. developed a microfluidic immunoarray platform for the multiplex and sensitive detection of parathyroid hormone-related peptides (PTHrP) in cancer diagnostics. This system was used to detect PTHrP 1-173, a key agent of HHM and implicated in cancer metastasis. Zhou et al. developed a platform for characterization and electrical impedance of human cancer cells, focusing on the deformability of breast cancer cells. Ren and colleagues developed a platform for capturing LNCaP-C4-2 prostate cancer cells, optimizing the capture ratio and limit. Zielke et al. used a microfluidic device for the isolation of cancer cell subpopulations based on single cell glycolysis, demonstrating a robust and easy way of single cell isolation. Malhotra et al. designed an ultrasensitive electrochemical microfluidic array for the detection of a four-protein panel of biomarker proteins, demonstrating high sensitivity in 50-minute assays. Another study investigated the mechanical phenotype of human colon adenocarcinoma cells, a heterogeneous cell line with multipotency and self-renewal abilities.

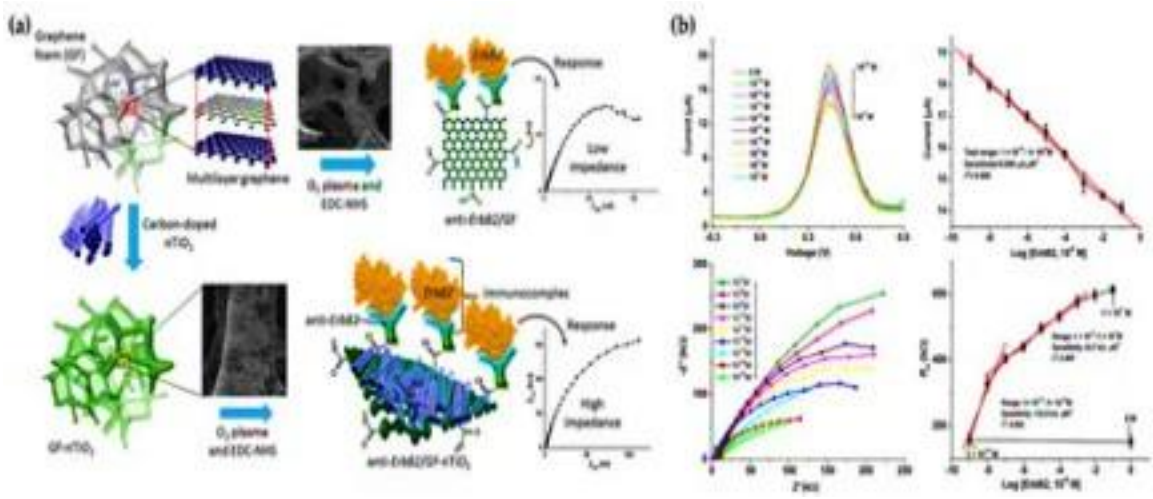

Figure 4. Phenotypic profiling of cancer cell subpopulations; (a) schematic showing the separation of cancer cells into four zones of a microfluidic device; (b) phenotypic analysis of isolated tumor cells [44].

A study developed a microfluidic system to mimic the microenvironment of ductal carcinoma in situ (DCIS), a stage where tumor cells remain inside the mammary duct. The system involved embedding a DCIS model cell line in a 3D hydrogel with mammary fibroblasts, followed by confocal microscopy, optical metabolic imaging, and nuclear magnetic resonance spectroscopy. The study found that DCIS cell metabolism led to hypoxia and nutrient starvation, revealing altered metabolism focused on glycolysis. Another study designed a femtomolar sensitivity and high-selectivity microfluidic immunosensor for real-time detection of epidermal growth factor receptor 2 proteins to quantify breast cancer.[45]

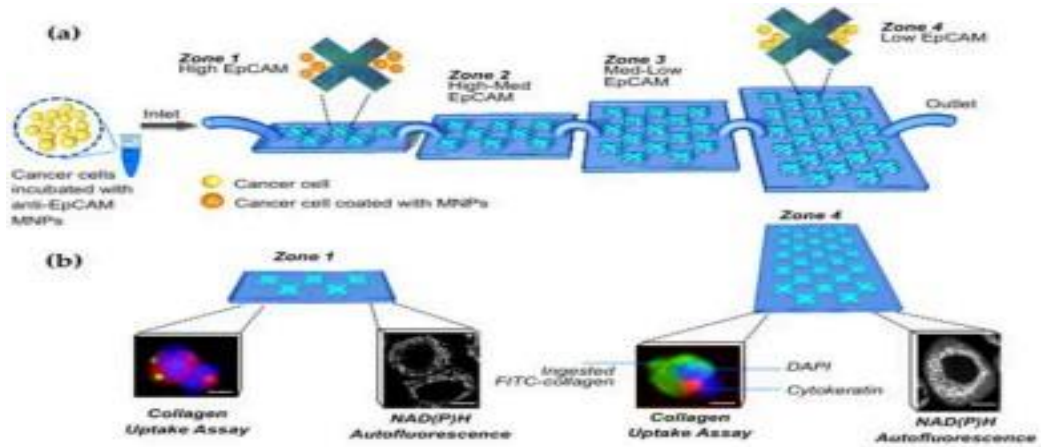

Figure 5. (a) Graphene foam (GF) and GF−nTiO2 electrodes; (b) DPV for different ErbB2 concentrations from 1.0 fM to 0.1 μM .

A study has developed a potential genosensor for detecting high-risk human papillomavirus (HPV) at low concentrations and distinguishing it from other common human malignancies. The genosensor, prepared using a microfluidic tool and an HPV16 capture DNA probe, has a limit of detection of 10.5 pM for complementary ssDNA HPV16 oligos. Current clinical tests are not routinely performed due to limitations and high costs.

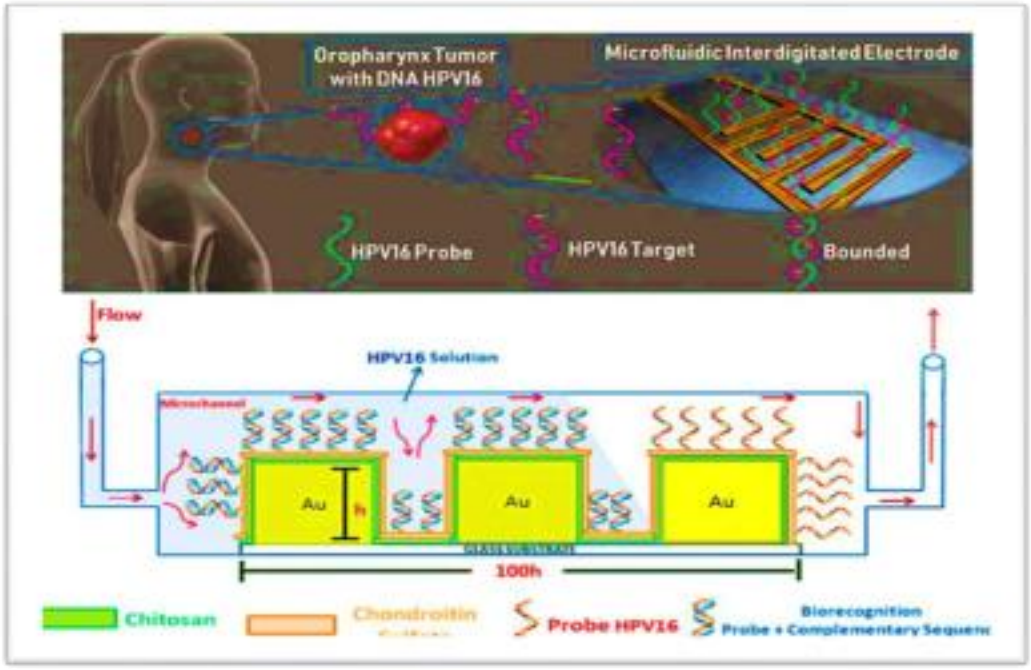

Figure 6. Schematic representation of the functionalization of the electrode and detection of HPV16 under continuous flow .

Oral cancer is a head and neck cancer, and a SMILE platform has been developed for early screening. The platform is sensitive, selective, and easy to use, and aims to reach many potential users and prevent the disease. It also has potential for cancer cell research from other body fluids like saliva. Tsai et al. developed an integrated microfluidic chip capable of detecting circulating tumor cells (CTCs) from human blood samples. The chip can detect OCCs vaccinated at concentrations of 100 cells.ml1 in human blood fluids, making it a promising tool for early diagnosis of ovarian cancer. As microfluidic systems become a key technology for cancer diagnostics, the study of this area is increasing, with low-cost sensitive systems enabling personalized medicine for cancer patients.

5. MICROFLUIDIC DEVICE

Microchannels and microcapillaries are two main types of devices used in particle production. Microchannel-based systems are manufactured using processes like micromilling, micromachining, lithography, or mold replication, allowing for the creation of small particle systems with uniform flow and droplet size. These systems are expensive and time-consuming, but can be used to produce large numbers of products. Capillary-based devices are made from inexpensive components and can be produced quickly and in high-pressure conditions. However, microchannel technology can lead to phase inversions, which can be avoided by selecting the right device for organic or aqueous droplets. Capillary-based devices prevent droplets from building the device's partitions and eliminate clogging issues. Advancements have allowed for the creation of microfluidic devices with various materials and geometries, allowing for novel physical properties and behaviors. Laser cutters and knife plotters are commonly used for

cutting in laboratory settings for prototyping.[50-54]

6. CONCLUSION

This review discusses the use of microfluidics in drug delivery systems for cancer treatment. Microfluidics, a science of manipulating low quantities of fluids, is useful in drug administration due to its key features such as microchannels and microcapillaries. Various microfluidic tools are innovative for cancer diagnosis, including self-assembled systems, droplet-based carriers, nonspherical systems, and nucleic acid delivery systems. Microfluidic fabrication involves processes like chemical, mechanical, laser-based, three-dimensional printing, and technologies.

Microfluidics can also be used in personalized medicine to create unique cancer models for individual patients, enabling pre-administration testing of various pharmaceuticals.[54,55]

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