



Microfluidic chip-based nano-carrier-based drug delivery systems and their efficacy assessment using tumor organ chips

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Received: October 08, 2024 **Accepted:** November 18, 2024 **Published:** December 20, 2024

Cite this article: Sun Y, Jin F, Gao D. Microfluidic chip-based nano-carrier-based drug delivery systems and their efficacy assessment using tumor organ chips. BME Horiz. 2024;2:136. <https://doi.org/10.70401/bmeh.2024.136>

Abstract

This mini-review explores advancements in the synthesis of nano-carrier-based drug delivery systems (NDDS) using microfluidic chip technology and their evaluation using tumor organ-on-a-chip models. We discuss the principles and advantages of hydrodynamic fluid focusing and micromixer for synthesizing polymeric nano-carriers, highlighting their ability to precisely control particle size, shape, and surface properties. The functionalization of nano-carriers for targeted drug delivery is also explored, emphasizing the potential for personalized medicine. The review emphasizes the use of tumor organ-on-a-chip models for evaluating NDDS, highlighting their ability to simulate physiological environments and provide dynamic and controllable evaluation platforms. This approach holds great promise for enhancing our understanding of drug behaviors and accelerating the translation of nanomedicines from bench to bedside.

Keywords: Drug delivery system, microfluidic, nanoparticles, nano-carriers, polymeric, tumor organ chips

1. Introduction

The quest for effective drug delivery systems (DDS) is a cornerstone of modern medicine, as they play a pivotal role in ensuring that therapeutic agents reach their intended targets with precision, maximizing treatment efficacy while minimizing adverse effects. Traditional DDS, such as tablets, capsules, syrups, and ointments, have been the mainstays of pharmaceutical administration for decades. However, these methods are not without their limitations. They often suffer from poor bioavailability, fluctuations in plasma drug levels, and an inability to achieve sustained release, which can lead to suboptimal therapeutic outcomes^[1]. Furthermore, the lack of targeted delivery in these systems results in off-target effects, reducing the overall therapeutic efficiency and increasing the risk of side effects.

The field of nanomedicine has emerged as a transformative approach to overcoming these challenges. Nano-carrier-based drug delivery systems (NDDS) have shown great promise in enhancing therapeutic outcomes by offering improved drug stability, targeted delivery, and reduced side effects^[2,3]. However, the development of NDDS is not without its own set of challenges. The synthesis of these nano-carriers often faces difficulties in precisely controlling particle size distribution, achieving high encapsulation efficiency, and ensuring batch-to-batch reproducibility^[4]. These challenges can hinder the translation of NDDS from the lab to clinical use.

In recent years, microfluidic chip technology has risen to prominence as a solution to these synthetic challenges. It offers precise control over reaction conditions, enhances encapsulation efficiency, and improves batch-to-batch reproducibility, making it a promising approach for the synthesis of NDDS^[4]. Moreover, microfluidic techniques have the potential to revolutionize drug evaluation methods by providing a more accurate simulation of the complex physiological environment of the human body, which traditional methods like cell culture and animal experiments often fail to achieve^[5].

Among the various microfluidic applications, tumor-on-a-chip technology stands out as a powerful platform for evaluating NDDS. By



simulating physiological environments, it offers dynamic and controllable evaluation platforms that reduce the reliance on animal experiments and provide a more accurate assessment of NDDS penetration, distribution, and therapeutic efficacy within tumor tissue^[6]. This technology not only enhances our understanding of drug behavior but also accelerates the translation of nanomedicines from bench to bedside.

Thus in this review, we mainly focus on the synthesis of NDDS using microfluidic based methods and investigate the drug efficiency on tumor organ-on-a-chip models. Additionally, we will discuss the functionalization of nano-carriers for targeted drug delivery and the importance of simulating physiological environments for accurate drug evaluation.

2. Synthesis of Nano-carrier Drug Delivery Systems

2.1 Overview of nano-carriers

Nano-carriers are a class of microscopic delivery systems designed to encapsulate, protect, and precisely target drugs to specific sites within the body, thereby enhancing therapeutic efficacy while minimizing side effects^[7]. Among the various materials employed in the design of nano-carriers, polymeric materials such as liposomes, nanoparticles (NPs), and dendrimers have gained increasing attention. This is due to the fact that polymeric nano-carriers can conjugate drugs to the polymer matrix through cleavable linkers, providing more controlled drug release compared to traditional physical encapsulation methods^[8]. Moreover, the responsiveness of polymeric nano-carriers to stimuli associated with specific biological environments is a critical feature that enables highly efficient drug release^[9]. This precise targeting and stimulus-responsive release mechanism enhance the therapeutic efficacy of drugs while minimizing side effects, making polymeric nano-carriers an attractive option for advanced drug delivery systems.

Usually, nanoparticle synthesis for drug delivery can be categorized into bottom-up and top-down methods. Bottom-up involves assembling pre-existing polymers, like emulsification, to create homogeneous dispersions^[10]. Top-down methods, such as self-assembly and nanoprecipitation^[11], directly synthesize NPs from larger materials. However, these methods often struggle with precise size control due to factors like the complexity of the chemical reactions involved and the difficulty in uniformly dispersing reactants, which can lead to a wide particle size distribution. This variability can affect the consistency and predictability of drug release. In contrast, microfluidics offers a more controlled environment for nanoparticle synthesis, allowing for a narrower and more uniform size distribution by precisely controlling reaction conditions^[12]. This precision is crucial for enhancing the reliability of drug delivery systems. Moreover, traditional encapsulation methods may have low encapsulation efficiency, whereas microfluidic technology can provide a more accurate mixing ratio of drugs and polymers, thereby improving encapsulation efficiency and drug loading. Through precise control of the mixing process, microfluidic technology ensures that drugs are uniformly distributed within NPs. With its advanced automation and precision control, microfluidics significantly enhances consistency and reproducibility across batches. Consequently, employing microfluidics for synthesizing NDDSs represents a promising and innovative direction in pharmaceutical development.

2.2 Methods for synthesizing nano-carriers on chip

In microfluidic synthesis systems, the dynamics of fluid flow play a pivotal role in the synthesis of nanomaterials. In this session, we will introduce the methods based on the form of fluid mixing, dividing them into flow focusing and micromixer types.

2.2.1 Hydrodynamic fluid focusing (HFF)

HFF involves the manipulation of fluid streams to concentrate a sample within a specific region of the microfluidic channel. To better understand the fundamental principles of HFF in microfluidics for drug encapsulation within polymeric NPs to achieve higher drug loading, Li *et al.*^[13] presented an approach that integrated computational fluid dynamics with experimental validation to elucidate the fundamental mechanisms of drug encapsulation within polymeric NPs through microfluidic-based nanoprecipitation. Their study resulted in curcumin-loaded polymeric NPs with a drug loading (DL) of 2.6% and an encapsulation efficiency (EE) of 77.3%. Furthermore, Rezvantala *et al.*^[14] utilized molecular dynamics simulations to investigate the impact of microfluidic technology at the molecular level. They proposed a conceptual “interface” mechanism for microfluidic self-assembly at the atomic scale, significantly advancing the understanding and optimization of NPs synthesis on microfluidic systems (Figure 1). Additionally, Abdelkarim *et al.*^[15] explored the influence of channel geometry on the nanoprecipitation process of poly(lactic-co-glycolic) acid (PLGA) NPs. By testing ten different channel designs varying in length, aspect ratio, number of interfaces, and curvature, they found that while channel length had minimal impact, increasing the diffusion area and incorporating curvature significantly reduced particle size. These findings suggested that modifying channel geometry is an effective strategy to control NP size, providing a straightforward design adjustment that can be easily integrated into microfluidic devices. Building on these insights, Fabozzi *et al.*^[16] investigated the effects of process parameters on the preparation and optimization of poly(lactic-co-glycolic acid)-poloxamers NPs formulations (PLGA/PF68 + PF127 NPs) decorated with hyaluronic acid (HA) for intravenous delivery of a model chemotherapeutic agent, irinotecan, using HFF. The optimized HA-based NPs formulation exhibited a spherical morphology, with a core-shell structure, small hydrodynamic diameter (approximately 120 nm), uniform size distribution (PDI < 0.06), and high and high DL (22.7%), drug EE (87.8%), and yield (92.4%). In conclusion, the method of synthesizing nano-carriers through HFF in microfluidics offers higher EE, and the resulting NPs exhibit

narrower size distribution and more uniform dispersion.

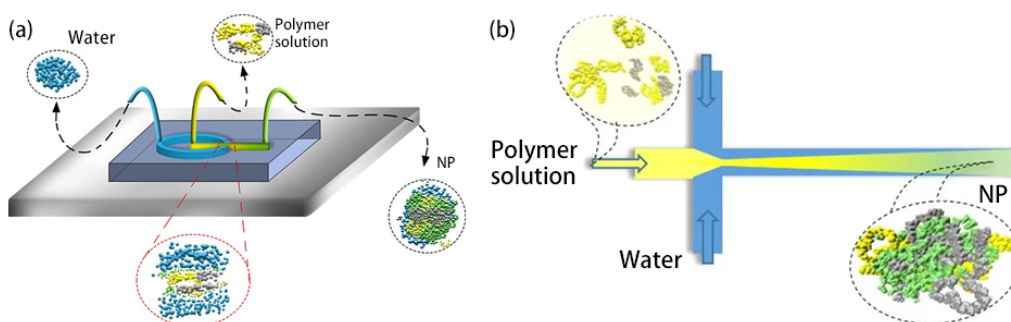


Figure 1. HFF method for synthesizing NDDS. (a) Utilized HFF to synthesize polymeric NDDS; (b) Represented schematic illustration of the scenario for the synthesize polymeric NDDS^[14]. HFF: hydrodynamic fluid focusing; NDDS: nano-carrier-based drug delivery systems; NP: nanoparticle.

2.2.2 Micromixers

Micromixers, on the other hand, are designed to induce rapid mixing of fluids by breaking up the slow diffusion between molecules. On microfluidics, passive micromixers are the predominant choice, favored for their simplicity and minimal impact on samples. These devices rely on structural innovations to generate vortices and perturb fluid flow within the channel. Tiboni *et al.*^[17] utilized three-dimensional (3D) printing to fabricate two distinct types of microfluidic chips, namely the “serrated” relief (Figure 2a) and the “split and recombination” designs (Figure 2b). These microfluidic chips facilitate passive micromixing within the channels. They also used cannabidiol as a model drug to assess the impact of manufacturing parameters on the characteristics of the final nanocarriers. This method could effectively produce both polymeric and lipid-based nanocarriers. Le *et al.*^[18] presented a 3D microfluidic Tesla mixer with high mixing performance, which further enhanced the encapsulation of curcumin. This device allowed for the controlled formulation of PLGA NPs with size of 79.2–196.3 nm and a PDI value < 0.1. And this device achieved considerable higher EE (68.40%) and DL (43.01%) than bulk mixers. There is also a Staggered Herringbone Mixer. Essa *et al.*^[19] prepared polymeric NPs by using a benchtop Nanoassembler (Figure 2c). The Nanoassembler utilizes microchannels in a cartridge that allows for the mixing of organic and aqueous phase in precisely controlled speeds and ratios under laminar flow. They found a concentration of organic phase polymer which was shown to produce relatively low particle size using this instrument. Additionally, droplet can be a micromixer to synthesize nanogels (NGs) as nano-carriers. Giannitellia *et al.*^[20] developed a microfluidic flow-focusing device with a pneumatic micro-actuator to NGs composed of hyaluronic acid and polyethyleneimine for controlled drug delivery. The actuator allowed real-time modulation of the microdroplet diameter, resulting in NGs with a tunable hydrodynamic diameter ranging from 92 to 190 nm and an extremely low polydispersity index of 0.015. The NGs demonstrated enhanced antitlastic effects *in vitro* against ovarian cancer cells when doxorubicin was used as a model drug. Micromixers ensure that reactions occur under uniform conditions, leading to high reproducibility of the assays.

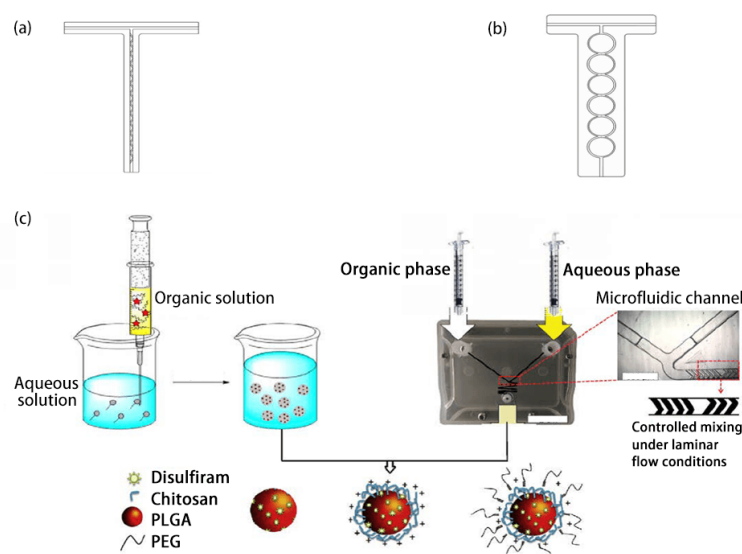


Figure 2. Micromixer microfluidic chips for synthesizing NDDS systems. (a) “Z” microfluidic chip; (b) “C” microfluidic chip. Republished with permission from Elsevier^[17]; (c) SHM micromixer method^[19]. NDDS: nano-carrier-based drug delivery systems; SHM: staggered herringbone mixer; Z: zigzag design; C: split and recombine design.

In fact, both HFF and micromixers represent passive mixing methods. Table 1 lists the two methods for synthesizing NDDS, which can achieve better nanoscale dimensions and higher EE DL values in microfluidic systems. Additionally, the reproducibility in microfluidics is also higher.

Table 1. Comparison of two methods for synthesizing NDDS.

Method	Polymer nanocarrier material	Encapsulated model drug	Size (nm)	Encapsulation Efficacy (%)	Drug-Loaded (%)	Ref
HFF	PEG-PLGA	Curcumin	60	77.3	2.6	[13]
	PLGA-PEG-RF	/	30	/	/	[14]
	PLGA	Rifampicin	93-100	10.0	/	[15]
	PLGA/PF68-PF127-HA	Irinotecan	120	87.8	22.7	[16]
Micromixer	PLGA	Cannabidiol	80-160	/	3.0	[17]
	PLGA	Curcumin	79-196	68.4	43.0	[18]
	PLGA-chitosan-PEG	Disulfiram	179	78.7	/	[19]
	HA-Polyethyleneimine	Doxorubicin	92-190	/	/	[20]

NDDS: nano-carrier-based drug delivery systems; HFF: hydrodynamic fluid focusing; PEG: poly(ethylene glycol); PLGA: poly(lactic-co-glycolic) acid; PEG-PLGA: poly(ethylene glycol)-poly(lactic-co-glycolic) acid; PLGA-PG-RF: riboflavin (RF)-targeted poly(lactic-co-7 glycolic acid)-poly(ethylene glycol); PLGA/PF68-PF127-HA: poly(lactic-co-glycolic acid)-poloxamers NPs formulations decorated with hyaluronic acid; HA-Polyethyleneimine: hyaluronic acid polyethyleneimine.

2.3 Functionalization of nano-carriers for targeted delivery

In drug delivery, the ability to target specific cells or tissues is crucial for maximizing therapeutic efficacy while minimizing side effects. Microfluidics also enables the synthesis of functionalized, targetable nano-carriers for precise drug delivery. Due to the pH difference between the tumor microenvironment and normal physiological conditions, with the former typically being more acidic, researchers have designed numerous pH-responsive NDDS for targeted cancer therapy. Khademzadeh *et al.*^[21] utilized a microfluidic aerosol-assisted method to synthesize a pH-responsive nano-carrier using chitosan and glutaraldehyde. This nano-carrier demonstrated an EE of 77.8% and a size of 18.5 nm. The maximum release percentage of gefitinib was 47.77% at pH 5.5, and 31.43% at pH 7.4. Although this study produced nano-carriers with good EE, the drug release rate in response to pH changes was relatively low and the duration was short, with a release rate of 47.7% observed within the first 24 h. In contrast, Alizadeh *et al.*^[22] synthesized a pH-sensitive nano-carrier for the anticancer drug gefitinib using microfluidics assisted self-assembly of alginate and chitosan. Despite having a lower EE of 68.4%, the synthesized nano-carriers were 5.3 nm in size and exhibited a maximum release rate of over 50% at pH 5.5, while less than 10% at pH 7.5. This research demonstrated better pH responsiveness and a higher drug release rate, with a slower release velocity and longer duration, maintaining a sustained release for over 120 h. The EE values in these studies did not exceed 80%. Bai *et al.*^[23] successfully synthesized hydroxyl-FK866-PLGA NPs using a hydrodynamic flow-focusing microfluidic system, achieving high EE of $98.6 \pm 5.8\%$. These NPs demonstrated pH-responsive drug release, with 60% EE maintained at pH 6.4 over two months, and less than 40% at pH 7.4, indicating faster release under acidic conditions typical of tumors. The sustained release pattern without initial burst was observed across pH 6.4 to 8.4, suggesting drug release is primarily through hydrolysis between hydroxyl-FK866 and PLGA rather than diffusion. Despite the pH sensitivity, improving tumor tissue targeting and reducing damage to normal tissues remains a critical area for further research. Despite the pH sensitivity of these studies, further improving the targeting and selectivity of the tumor tissue while reducing damage to normal tissues remains crucial. Introducing targeting ligands or antibodies on the surface of NPs can enhance their targeting of cancer cells. Yang *et al.*^[24] developed a one-step self-assembly microfluidic method to fabricate biocompatible core-shell nano-capsules with surface functionalities that can interact with tumor cell receptors (Figure 3). After co-culturing with KPC cells for 5 h, the group treated with Nile Red-loaded PCL-PEG-FA nano-capsules (NR@PCL-PEG-FA) exhibited a significantly higher fluorescence signal compared to those with free Nile Red and Nile Red encapsulated in PCL nano-capsules (NR@PCL). Quantitative analysis using flow cytometry also confirmed that the fluorescence intensity of KPC cells co-cultured with NR@PCL-PEG-FA was markedly higher than those in other groups, indicating the precise tumor targeting of these nano-capsules. Future research could also consider combining other stimulus-responsiveness (such as temperature, light, enzymes, etc.) to enhance the multifunctionality of drug carriers.

3. Application of Microfluidic Based Tumor Model for Drug Efficacy Evaluation

3.1 Definition and significance of organ-on-a-chip technology

The rapid advancements in NDDS research necessitate a parallel evolution in ex vivo models for evaluating the efficacy and safety of nanotherapies within human physiological systems. While there are several methods for evaluating NDDS, including traditional two-dimensional (2D) cell cultures, animal models, and more recently developed organoid cultures, and organ-on-a-chip models.

Organ-on-a-chip are microfluidic devices that aim to replicate the microenvironment of human organs and tissues. They replicate the structural and functional complexities of human tissues and organ units, addressing the limitations of conventional cell cultures and offering a potential alternative to animal testing^[25]. The technology allows for precise manipulation of cellular microenvironments, including the application of shear stress, regulation of oxygen levels^[26], and exposure to various biochemical cues, which are critical for the accurately assessing NP interactions. Furthermore, organ-on-a-chip models support personalized medicine approaches by facilitating studies with patient-derived cells^[27]. The ability to mimic the multifaceted nature of human systems renders this technology invaluable for predicting the behavior of nanotherapies in a more accurate and ethical manner than traditional animal models^[28] thus accelerating the translation of nanomedicines from bench to bedside.

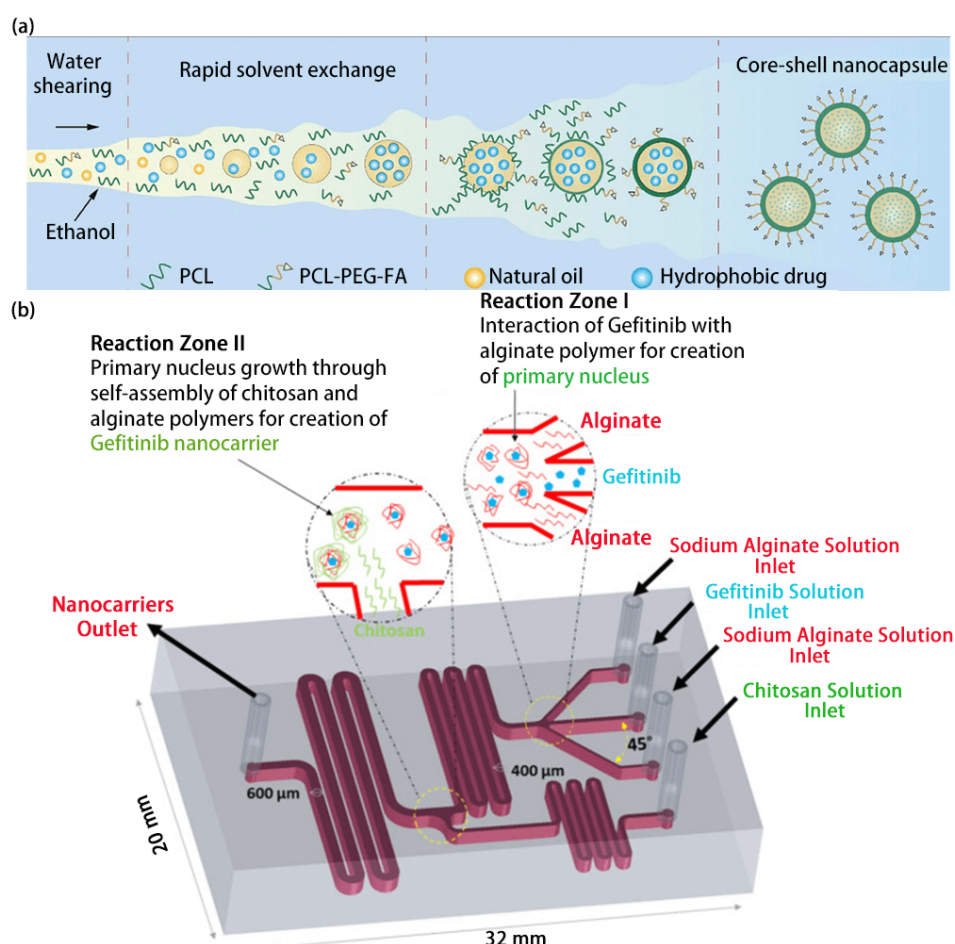


Figure 3. Microfluidic synthesis of functionalized NDDS. (a) Biocompatible core-shell polymer nanocapsules with tunable surface functionalities are synthesized through rapid mixing self-assembly co-precipitation in microfluidic channels. Republished with permission from John Wiley and Sons^[24]; (b) Microfluidic chips used for the synthesis of pH-responsive polymeric NDDS (surface-coated with chitosan that can respond to pH changes)^[22]. NDDS: nano-carrier-based drug delivery systems; PCL: biodegradable and hydrophobic poly(ϵ -caprolactone); FA: folic acid; PEG: poly(ethylene glycol).

3.2 Tumor organ chips used for drug efficacy studies

Cancer is one of the leading causes of mortality globally, underscoring the critical need for precise efficacy assessment of tumor drugs a post-development. Nano-carriers, as delivery systems for tumor drugs, must be rigorously evaluated within a simulated tumor microenvironment to ensure their effectiveness. Tumor organ-on-a-chip technology provides an innovative *in vitro* platform that can replicate the 3D tissue architecture of tumors, providing a more accurate reflection of the *in vivo* state of tumor cells compared to traditional 2D cell cultures^[29,30]. Martins *et al.*^[31] developed a microfluidic device that simulates the spatial organization of brain tumors. Human glioblastoma multiforme (U87-MG) cells were 3D cultured within PAGEXXatrigel on chip and exposed to different doses of free docetaxel (DTXL), DTXL-loaded spherical polymeric NPs (DTXL-SPN), and aromatic N-glycoside N-(9-fluorenylmethoxycarbonyl)-glucamine-6-phosphate (Fmoc-Glc6P). The study found that brain tumor cells were more sensitive to DTXL treatment compared to traditional cell monolayers, with an IC₅₀ value 50 times lower, indicating that the microfluidic chip can reproduce the 3D spatial arrangement of solid tumors. Additionally, the study evaluated the cytotoxicity of DTXL-SPN and found that at 24 h, the cell viability was $69 \pm 30\%$ for DTXL-SPN versus $80 \pm 7\%$ for free DTXL. This decreased to $64 \pm 12\%$ vs $57 \pm 1\%$ at 48 h and to $56 \pm 17\%$ vs $40 \pm 1\%$ at 72 h for DTXL-SPN and free DTXL, respectively, demonstrating the enhanced drug delivery capability of the

nano-carrier system. The tumor chip model also simulates dynamic processes that are challenging to achieve in traditional 2D cultures. Kim *et al.*^[32], utilized a microfluidic hepatocarcinoma chip to assess the cellular efficacy and real-time reactive oxygen species generation of anticancer drug-loaded NPs under both static and dynamic conditions. Tumor organ-on-a-chip technology can also simulate critical features of the tumor microenvironment, such as dense cell networks and extracellular matrix (ECM)^[33], which represent significant bottlenecks for nano-carriers during tumor delivery. These features are crucial for assessing the penetration, distribution, and efficacy of NDDS in cancer treatment. Olea *et al.*^[34] investigated the mobility of polymeric micelles within an *in vitro* tumor model, focusing on the challenges faced by micellar nano-carriers when navigating the dense ECM of tumors. Using a microfluidic chip with dual-ECM configurations and MCF7 spheroids, the study investigated the distribution and dynamics of micelles in different ECMs through confocal microscopy imaging, evaluating the interactions between biological interfaces and polymeric micelles. This research underscores the potential of simple test models to significantly enhance the understanding of tumor drug delivery systems, providing a more efficient feedback loop between formulation and testing. Moreover, the stability of NDDS is also crucial. Deng *et al.*^[35] introduced a microfluidic tumor-on-a-chip model that recreated the tumor milieu, allowing for in-depth investigation of the diffusion, cellular uptake, and stability of single-chain polymeric nanoparticles (SCPNs). The chip (Figure 4) was utilized to assess the impact of the polymer's microstructure on the behavior of SCPN when crossing the ECM and on their internalization in 3D cancer cells. This 3D microfluidic platform provides a valuable tool for understanding the relationship between polymer microstructure and SCPN stability, which is crucial for the rational design of NPs for targeted biological applications.

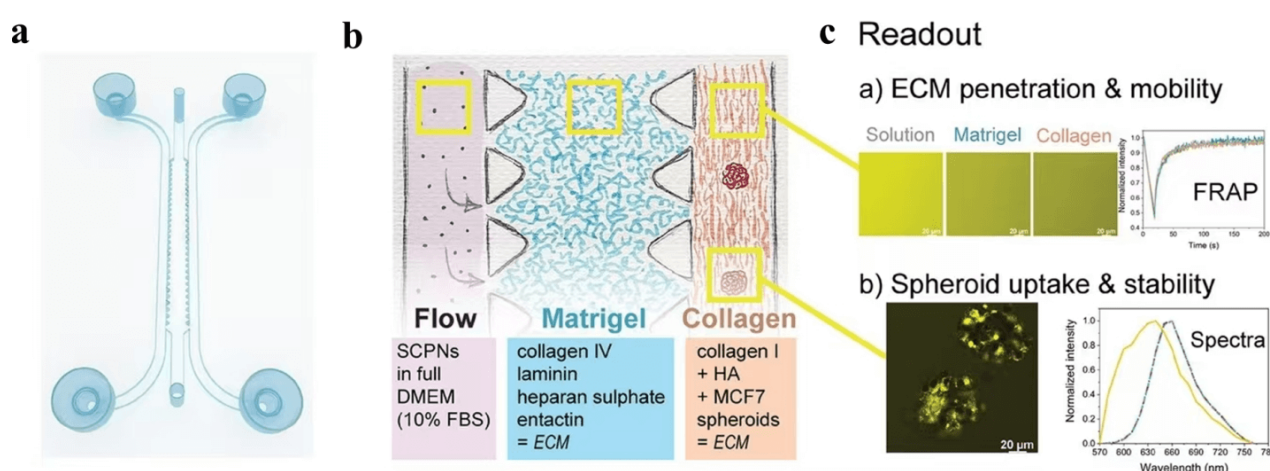


Figure 4. (a) The commercial microfluidic chip DAX1 from AIM Biotech. The chip contains three channels separated by triangular pillars; (b) ECM constructed from Matrigel is added to the middle channel. A mix of collagen type I and hyaluronic acid with embedded MCF7 spheroids is added to the right channel, to represent the tumor environment. In the remaining left channel, the solution of SCPNs in full DMEM media (10% FBS) is added and allowed to diffuse for 24 h; (c) As readout, the ECM penetration, spheroid uptake, as well as stability of NPs are assessed in different chip locations. SCPNs diffusion is evaluated by FRAP technique. The uptake and stability of SCPNs in MCF7 spheroids are studied by emission intensity and wavelength shift of Nile Red. Reproduced with permission from John Wiley and Sons^[35]. ECM: extracellular matrix; SCPNs: single-chain polymeric nanoparticles; FBS: fetal bovine serum; FRAP: fluorescence recovery after photobleaching; DMEM: Dulbecco's modified eagle's medium.

In summary, tumor organ-on-a-chip technology superior evaluation of the stability and penetration, distribution of nano-carriers compared to traditional cell cultures. However, validating the physiological and clinical relevance of *in vitro* study results using organ-on-a-chip models remains a significant challenge. Future advancements may include multi-organ models for more accurate simulations.

4. Conclusion and Future Perspectives

The drug delivery systems have seen remarkable advancements with the advent of nanotechnology and microfluidic chip technology. This mini-review delves into the synthesis of nano-carriers in microfluidic environments and the application of tumor organ-on-a-chip technology for drug efficacy evaluation. The HFF and micromixer allow precise control over nano-carrier properties, which is crucial for *in vivo* behavior and targeting. The potential clinical translation of these nano-carriers for personalized medicine is significant, offering tailored treatments to individual patient needs. Additionally, most current nano-drug delivery systems carry only a single drug, and mono-drug therapy is often insufficient. In the future, the controlled synthesis of dual-drug loaded NPs^[36] will also be a significant challenge.

Organ-on-a-chip technology has emerged as a powerful tool for evaluating drug and drug delivery systems' efficacy. The tumor-on-a-chip model provides a controlled environment mimicking physiological conditions, enabling more accurate assessments of NDDS. However, the single tumor-on-a-chip model has limitations in simulating multi-organ interactions and pharmacokinetics^[37]. The increasing research into multi-organ chip systems addresses this gap, promising more precise simulation assessments in the future^[38,39].

Looking ahead, future research directions could focus on optimizing nano-carrier designs for enhanced stability and targeting within the body. Additionally, the integration of multi-organ chip systems will be pivotal in predicting clinical drug responses more accurately. The collaboration across disciplines, including materials science, biomedical engineering, cell biology, biophysics, and oncology, is imperative for the advancement of these technologies from bench to bedside, ensuring more effective and targeted cancer treatments reach patients.

Declarations

Authors contribution

Sun Y: Writing-original draft preparation, writing-review and editing.

Jin F: Writing-review and editing.

Gao D: Supervision, project administration and funding acquisition.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

This work was financially supported by Natural Science Foundation of Guangdong Province (No. 2022A1515011437).

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