Chapter

A Microfluidic Device as a Drug Carrier

Fikadu Ejeta

Abstract

The development of nanomedicine or medical nanotechnology, has brought important new ways to the development of medicines and biotechnology products. As a result of groundbreaking discoveries in the use of nanoscale materials significant commercialization initiatives have been launched and are at the forefront of the rapidly expanding field of nanotechnology by using smart particles. Microfluidic technologies use nano-and micro-scale manufacturing technologies to develop controlled and reproducible liquid microenvironments. Lead compounds with controlled physicochemical properties can be obtained using microfluidics, characterized by high productivity, and evaluated by biomimetic methods. Microfluidics, for example, can not only produce nanoparticles in a well-controlled, reproducible, and high-throughput manner, but it can also continuously create three-dimensional environments to mimic physiological and/or pathological processes. Materials with smart properties can be manipulated to respond in a controllable and reversible way, modifying some of their properties as a result of external stimuli such as mechanical stress or a certain temperature. All in all, microfluidic technology offers a potential platform for the rapid synthesis of various novel drug delivery systems. Therefore, these smart particles are equally necessary as the drug in drug delivery.

Keywords: smart materials, nanomedicine, microfluidic devices, drug delivery, nanocarriers

1. Introduction

Nanomedicine is a branch of medicine. Its goal is to use nanotechnology—manipulation and manufacturing of materials and devices with diameters of 1–100 nanometers—to prevent diseases and imaging, diagnose, monitor, treat, repair, and regenerate biological systems [1]. The development of nanomedicine or medical nanotechnology, has brought important new ways to the development of medicines and biotechnology products [2]. As a result of groundbreaking discoveries in the use of nanoscale materials significant commercialization, initiatives have been launched and are at the forefront of the rapidly expanding field of nanotechnology [3, 4], and they are expected to overcome the continuing challenges of ineffective drug delivery systems [5].

Materials with smart properties can be manipulated to respond in a controllable and reversible way, modifying some of their properties as a result of external stimuli such as mechanical stress or a certain temperature. Because of their small size, customizable chemical surface qualities, high volume-to-surface ratio, and, fundamentally, the ability to load active medicinal components and imaging agents, nanoparticulate drug delivery has been discovered to successfully affect nanomedicine [6]. In addition, nano-drug delivery media have been proven to improve beneficial results or effects, and reduce the side effects associated with drugs that have already been approved on the market, enabling new treatment methods and inspiring further improvements in the undesirable drug properties of active biological products. Research that was previously considered undeveloped [7].

Microfluidic technologies use nano-and micro-scale manufacturing technologies to develop controlled and reproducible liquid microenvironments [8, 9]. Lead compounds with controlled physicochemical properties can be obtained using microfluidics, characterized by high productivity, and evaluated by the biomimetic method *in vitro* for a human organ on a chip [8, 10]. The microfluidic generation has become an efficient device for the manufacture of microparticles with controlled morphology and preferred properties due to its ability to precisely control the emulsification procedure and generate droplets of monodisperse compounds in microchannels [11]. Microfluidics' ability to produce double emulsions having one, two, three, or more numbers of droplets with remarkable precision displays the degree of control it provides [12]. Since the size of the particles has a substantial influence on carrier release profile [13], it's crucial to place together polymer matrix with appropriate sizes and size distributions to accurately regulate the release of payloads. The loading of medicines onto the polymeric matrix and the release of payloads can both be controlled by changing their interior structures [14]. Multiple medication delivery can be achieved by altering the size and number of interior partitions [14, 15]. Another way to control the release of the payload is to synthesize polymer fragments by using stimulus-responsive substances [16]. After the environmental triggers (including pH, temperature, or ionic strength) are disclosed, the fragments will pass through physicochemical alternatives and then release the payload [17, 18].

Microfluidic technology has advantages in terms of small particle size distribution, lower polydispersity index, higher packaging and loading efficiency, better batch-to-batch uniformity, and the possibility of easy scaling [19]. Interestingly, the preparation of microfluidic chips is simple and easy to implement, thus realizing the economical production of nanocarriers [20]. Various microfluidic chips have been manufactured to synthesize organic, inorganic, polymer, lipid-based vesicular and hybrid nanocarriers [21]. All in all, microfluidic technology offers a potential platform for the rapid synthesis of various novel drug delivery systems [22].

The manufacturing processes for polymer microparticles are becoming increasingly important for applications such as the controlled release of active ingredients, medical-diagnostic tests, the achievement of superhydrophobic surfaces, the optimal design of impact-resistant polymer composites, and food technology [23].

Polymer microparticles are produced using a variety of processes, including suspension or emulsion polymerization, solvent evaporation, spray drying, small-hole spraying of polymer solution and the Shirasu porous glass membrane (SPG) emulsification method. On the other hand, traditional manufacturing processes have several disadvantages, including the fact that they take time, cause particle coalescence, and lead to non-uniform particle sizes and shape irregularities [24]. To work around these limitations, you can use the electrospray method. Furthermore, the electrospray

technique offers many benefits over earlier approaches, including minimal residue, the use of very few solvents, low cost, and the use of high molecular weight polymers [25]. The microdevices are made up of two flow-focusing pads that work together in a two-step procedure to make double emulsions. As a result, at low flow rates, the aqueous phase is symmetrically restricted at the initial connection point as a result of which monodisperse aqueous monomer plugs are formed. The oil phase encapsulates liquids 1 and 2 at the second connection point and creates double droplets of aqueous and monomeric phases. The composite droplets then reach a third junction where the channel cross-section is enlarged, whereby they assume spherical shapes. In the large section, conservation of mass forces the droplets to slow down significantly, thereby decreasing the spacing between successive droplets and thus decreasing the spacing between successive droplets, thereby decreasing the spacing between successive droplets [26].

Advances in drug delivery technology can improve pharmacological factors, including efficacy and bioavailability, to discover and develop more effective drugs to improve the treatment effects and quality of life of patients. Manufacturing quality control, fluctuations between product batches, and the inability to obtain physiologically relevant test results in traditional *in vitro* prescreening platforms are all obstacles to nanoparticle drug delivery [10]. Microfluidics has evolved from microliter fluid processing to nanoliter fluid processing, including multidisciplinary methods that can be used in a wide range of applications [27, 28]. Microfluidics (a method of fabrication) provides a mechanism for making highly controllable, reproducible, and scalable methods to produce nanoparticles. When compared to traditional *in vitro* culture methods, the organ-on-chip microfluidic technology provides highly relevant organ-specific testing platforms capable of biologically relevant experimental time scales while employing a fraction of the sample and media volumes [29, 30].

Microfluidic technologies provide low-cost, simple-to-use platforms to control the flow of fluids. Emulsions produced in microfluidic devices have been used in a variety of scientific applications, comprising biomedical field, chemical synthesis, fluid flow, and controlled drugs delivery. T-junctions and flow-focusing nozzles are two types of microfluidic platform devices that are used to make emulsions [31, 32]. Both procedures allow for the production of monodisperse particles as well as a wide range of emulsion sizes. Flow-focusing devices are commonly used to produce monodisperse polymer particles, both spherical and non-spherical. FF devices have been proven to generate photo-curable polymeric particles, ion-cross-linkable thermosensitive gels, polymer-encapsulated cells, and other particles in some situations [33, 34], polymer-encapsulated cells [35, 36], and other particles [21, 37]. Microfluidics can be applied to polylactide particles to make the production of novel drugs easier.

2. Microfluidic devices

There are two main types of microfluidic devices for particle production: microchannels and microcapillaries [38]. Microchannel-based devices are commonly manufactured through processes such as micro-milling, micro-machining, lithography, and shape replication. In such devices, minimizing the interfacial environment causes spontaneous droplet formation, and therefore the droplet size is best dependent on the microchannel geometry while maintaining the oil phase flow rate within an optimal range. Total devices based entirely on microchannels are costly and time-consuming to manufacture, but they enable microsystems to be manufactured with

a particle size of only a few tens of micrometers. In addition, the microchannels in such devices can be properly aligned and, in addition to the uniform flow and strong liquefaction of certain droplets or the splitting of droplets to a uniform size, they can serve their equipment, and the systems can be expanded to produce a large number of products. In addition, structures mainly based on capillaries are usually made of low-cost components available on the market and can become microchannels in particle manufacturing. Importantly, these systems can be manufactured in a shorter time and can operate under harsh process conditions [39]. In a complete device based on microchannels, the dispersed phase is very close to the tool wall before being emulsified by the continuous phase, which may cause phase inversion [40]. Although, the affinity of the dispersed relative substance is greater than that of the continuous phase, the dispersed phase preferentially wets the partitions of the tool. This makes the selection of materials produced by the equipment more important than all other materials. However, phase inversion can be avoided by deciding which equipment is suitable for water droplets or organic droplets [41]. On the other hand, capillary-primarily based devices are tremendous for such terms. Here, the droplets are stopped from assembling the device's partitions. Capillary-specific devices allow for the manufacture of oil-in-water or water-in-oil emulsions with a single microsystem [42].

Using a variety of materials and shapes in microfluidic devices to allow future and desirable sort of physical activity and features. Each layer of a laminated microfluidic device is cut separately. The cutting process has a considerable impact on the device's dimensions and functionality. For prototyping and laboratory settings, due to the speed and simplicity each tool offers, cutting is usually done with a knife plotter (i.e., xurography) or laser cutter. A knife plotter works by precisely cutting material with a blade to create the geometry, while a laser cutter uses a focused beam (traditionally, CO_2 lasers are used) [43, 44]. Under these conditions, the droplet diameter can be reduced by increasing the flow rate, density ratio, and viscosity [45]. Bottom-up

***In vitro* culture**	**Advantages**	**Disadvantages**	**Reference**
2D cell culture	Cell cultures are laboratory dishes that are used to grow cells. They are flat and are usually made out of plastic. By sticking cells onto these dishes, scientists are able to study cell behavior using cheap materials. There are several protocols and extensive literature available to analyze data and understand cell behavior.	Limit the simulation of complex cell-cell and cell-matrix interactions to study cell behavior	[48–51]
3D cell culture	Increasing the cell's ability to organize tissue, to express different functions, and improving live imaging.	The cells in the *in vivo* system are in the body, so the *in vitro* system is not exactly like the *in vivo* system when testing cells in a dish.	[10, 52]
(Organ-on-a-chip)	Physiological effects of different tissue types and structures, such as cells and blood vessels, are recreated in a system of fluid and particles to generate forces.	This experiment is very difficult to do and will likely yield inconclusive results, because different humans react differently to the same stimuli.	[29, 53]

Table 1.
Advantages and disadvantages of the methods used in invitro drug screening by microfluidics.

technologies that rely on emulsion or self-assembly on the shape of the equipment used do not always provide fine, pre-designed control over particle geometry (shape, aspect ratio) and composition [46]. A microchannel flow-focusing system (EDCl) was used to study the manufacture of HANP cross-linked with adipic acid hydrazide (ADH) and chlorinated carbodiimide. The focus of this work is to analyze the process parameters of this unique method, which is a continuous nanoprecipitation at the water-organic solvent interface. The influence of the type of organic solvent used, the flow rate of the non-solvent, and the content of hyaluronic acid (HA) on the HANP characteristics of (hyaluronic acid nanoparticles) [47]. Several studies have found that the affinity between water and organic solvents influences the average diameter of nanoparticles (NPs) via water diffusion and the rate of nanoprecipitation. When the non-solvent shows a moderate affinity for water, the polydispersity becomes narrower. In addition, since the process is regulated by convection, lower HA concentrations and higher isopropanol flow rates will produce smaller particles. Regardless of the organic solvent, flow rate, or HA concentration, some stable NPs are formed. The process was found to be simple, repeatable, and fast. This process is expected to be used in the manufacture of oil-free HANP, which is important for medical, pharmacological, and cosmetic applications, as shown in **Table 1** [45, 47].

3. Synthesis of microfluidic nanocarriers

Beyond that, it seems that pharmaceutical formulators have been more interested in using synthetic nanocarriers than natural nanocarriers and colloidal systems, which have not been of much interest. Scientists have recently paid a lot of attention to the production of organic nano-carriers, particularly in pharmaceuticals, as pharmaceutical scientists have begun to recognize the important properties they confer on nano-carriers by microfluidic methods [21, 54]. Nano-carriers are created by spreading premade polymers or inducing polymers to develop through monomer reactions. These nanocarriers can be advanced in a variety of ways, and they are divided into classes based on the processes involved. In the primary group, materials are emulsified, but not necessarily in the other categories. As a result, it gives a straightforward and straightforward synthesis process. When those tactics are applied in typical devices, there is a lack of control over uniform blending, formation, and better impacts on formulation ingredients, and few goods have an excessive particle size dispersion as a result. Microfluidic control structures, on the other hand, can provide control over the aforementioned elements due to their equally sized particles [55]. Lipid polymer hybrid nanoparticles have been merged into high-capacity nanocarriers.

The microfluidic co-flow nanoprecipitation technology has been used to make a large number of LPHNPs. With the help of dissolving poly (lactic-co-glycolic acid) (2 mg/ml) into acetonitrile as a natural phase, the internal fluid changed its ordered state. The outer fluid had a two-to-three mass ratio of lecithin and Distearoyl-sn-glycero-3-phosphoethanolamine-polyethylene glycol 2000 dissolved in 4 percent ethanol and responded in water. These characteristics define a drug's potential to be a good choice for treating breast cancer [21, 22, 55].

Water-to-oil emulsification in a paper-based microfluidic drug carrier results in unique open-channel microfluidics with the capacity to manage the flotation of both adequate and inadequate surface tension liquids. The open channel devices are shown to be effective in limiting a variety of lower surface tension oils at high and low

flow rates, allowing for microfluidic emulsification of water in oil in an open channel instrument. The droplets should be formed inside the channel with the aid of an adjustable speed of the continuous phases of the emulsified water and oil. Finally, an instrument has been turned to being used efficiently to synthesize remarkably monodisperse hydrogel microparticles that might contain a drug molecule.

Additional research into the drug delivery properties of manufactured products has yielded promising results. Open channel microfluidic devices have the potential to achieve a high level of fluid manipulation with fast and low-cost production [56]. Dopamine is used as a model drug to quantify electrochemical flow on paper-based devices in a dynamic microfluidic method. Combining electrochemical methods with microfluidic devices to achieve time-resolved detection of neuron-like PC12 cells cultured on filter paper Dopamine [57, 58]. After investigating the attachment of cells to the outside of the paper with a fluorescence microscope; dopamine drug delivery after stimulation with acetylcholine was investigated. As a result, the data collected by the device is consistent with single-cell statistics, demonstrating the effectiveness of the technique for high-throughput quantification of tissues or chemical targets on tissues [59] for higher-throughput quantification of chemical targets on tissues or organs-on-a-chip [58].

In general, microfluidic devices maintain many qualities in pharmaceutical science, consisting of appropriate doses, ideal drug delivery, site-targeted delivery, sustained release and controlled release, reduced repeated doses, and minimal side effects. To do so, these advantages are the key quality of the drug delivery system. Microfluidic technology has been routinely used in many active moiety carriers, direct drug delivery systems, high-throughput screening, and the production of polymers as superior carriers for additives and drugs. Cheaper and easily produced paper-based materials are good substrates that do solve several problems associated with transportation, filtration and storage, concentrators, valves, and multiplexing [59]. Going forward, creating microfluids on paper in controlled drug delivery programs can offer exciting opportunities to broaden the scope of the subject matter and support improved the scientific translation of drug delivery systems. A device for the controlled release of vinblastine (VBL) drug responsive to stimuli from magnetosensitive chitosan capsules, which is a magnetically sensitive device for controlled drug delivery, was developed by embedding superparamagnetic iron oxide (SPIO) nanoparticles (NPs) into a chitosan matrix and external magnet. Thus, the release rate, time, and dose of VBL released have become controlled by an exterior magnet. The prepared VBL and SPIO NPs-loaded chitosan microparticles were characterized and showed individual and distinctive controlled release patterns. In addition, droplet microfluidics, which is a unique technique for producing polymer spheres, has grown to be used for the manufacturing of monodispersed chitosan microparticles [60]. Because of their distinct physicochemical behavior and synergistic effects in the prevention and inhibition of colorectal cancer progression, atorvastatin and celecoxib were chosen as the version dosage form. For precisely controlled multidrug delivery, a microfluidic collection of monodisperse multistage pH-responsive polymer/porous silicone composites were developed [61]. Fabrication incorporating hypromerose succinate acetate, which does not dissolve in acidic conditions but incredibly dissolves in basic (alkaline) pH environments, is effective in preventing and suppressing the acceleration of colon and rectal cancers. Microcomposite [62] of Atorvastatin, which benefits from the larger pore volume of porous silicon (PSi), is first loaded into the PSi matrix and then encapsulated via microfluidics into pH-responsive polymer microparticles containing celecoxib, a multidrug obtained Road

Polymer/PSi microcomposite. The manufactured microcomposites were confirmed to have a monodisperse size distribution, multistage pH-response, a particular ratiometric controllable loading extent closer to the concurrently loaded drug molecules, and tailored-made drug release kinetics. This attractive microcomposite technology prevents payloads from being released at low pH values and promotes medicine delivery at higher pH values, and could be used to prevent and treat colon and rectum cancers in the future. Overall, the pH-responsive polymer/PSi-based fully micro composite [63] might be employed as a common platform for combining drug delivery systems for multiple drug compounds [61].

The preparation of monodisperse microparticles of a biodegradable polymer was carried out using an instrument for focusing a microfluidic flow for controlled drug delivery. The manufacture of monodisperse microparticles containing a drug from biodegradable polymers, the use of devices for focusing a microfluidic flow, and the drug delivery properties of these particles have been described [64]. The particle size ranges from 10 to 50 mm. These particles are practically monodispersed with a polydispersity index of 3.9% [65]. Bupivacaine (amphiphilic) is included in a biodegradable debris matrix to characterize the formulation as a model drug [65–67]. The kinetic evaluation suggests that drug release from these monodisperse microparticles is slower than conventional strategies with the same average size, but reveals a larger particle size distribution and, more importantly, a significant reduction in a primary burst than that found with traditional methods, as shown in **Figure 1** [65, 67]. The difference in the preliminary kinetics of drug release is explained by the even distribution of the drug within the particles created using microfluidic strategies. These results demonstrated the application of microfluidic flow-focusing to homogeneous particle system technology for drug delivery [65].

Recently, thermosensitive liposome-controlled release using a disposable microfluidic instrument was developed, with the release of the encapsulated drug from the liposome nanocarrier expected to increase local drug delivery while reducing the toxic effects of increased temperature. High Intensity Focused Ultrasound (HIFU) [68–71], microfluidic devices with micro-HIFU (MHIFU), allow simulation of the bulky HIFU transmission instrument with lower energy consumption and to control of the release of the investigated low-temperature liposomes (LTSL) [52, 72]. In addition, when transitioning to a local temperature of 41–43°C, the structure changes from a gel to a liquid crystal phase, and the encapsulated drug is released by an external hyperthermia source (such as a microwave or infrared radiation laser). The

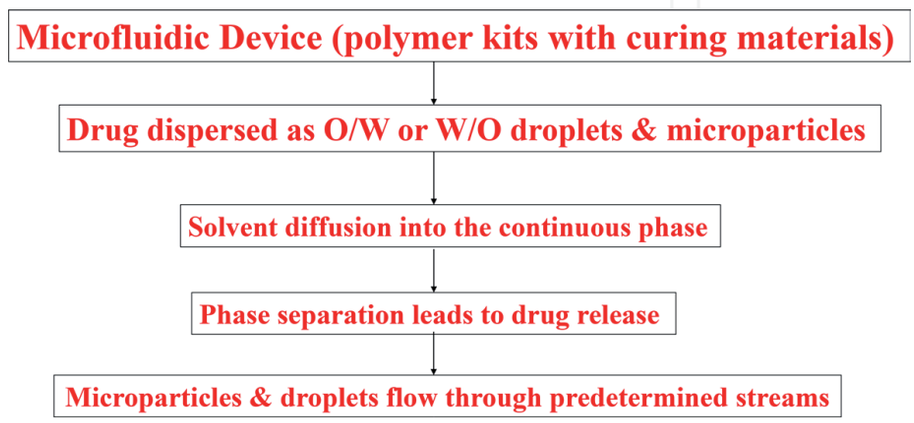

Figure 1.
A strategy for producing dispersed drugs using microfluidic techniques.

lipid membrane structure of low temperature-sensitive liposomes (LTSL) [73]. The era of microfluidics may also provide a promising method for studying ultrasound and the complex dynamics of organisms at the ultramicro level [74]. The main task of improving polymer nanoparticles for many procedures is to specifically engineer preferred physicochemical properties in a repeatable manner [67].

Microfluid self-assembly [9, 75] of polymer nanoparticles with adjustable compactness for controlled drug delivery is predominantly self-assembled hydrophobically modified chitosan (HMC) biopolymer-based nanos. The particle compactness can be determined by adjustable high-speed blending with hydrodynamic flow focusing on microfluidic channels. It has been demonstrated that the self-organizing properties of the chain can be controlled by optimizing the size and compactness of the species, as well as the more restricted particle size distribution, through various flow rates as well as the hydrophobicity of the chitosan chain of nanoparticles [67, 76]. The particle size of the formulation components increased with increasing blending time, while the chitosan produced smaller and more compact nanoparticles with a much smaller variety of aggregated chains and a higher degree of hydrophobicity.

The scientists found that nanoparticles with nearly equal forms of hydrophobic adhesion were formed by blending the two liquids. The scientists found that the lack of affinity for the aqueous medium and the blending times longer than the time of aggregation hindered the formation of nanoparticles with different forms of hydrophobic adhesion.

Moreover, researchers investigating the effectiveness of microfluidics for assembling HMCs and enclosing paclitaxel, a typical anticancer medication, showed that it has a significantly greater encapsulation efficiency and overall quality than the traditional bulk technique. The impact of the components of the synthetic medication on the parameters of the release of paclitaxel from nanoparticles was investigated. [31]. The predicted 50% paclitaxel diffusion coefficient upon drug release meant sustainability in controlling drug release for nanoparticle compactness and superior results compared to traditional bulk blending methods [31, 77]. These results show an excess of microfluidic methods for specific bottom-up control of the physicochemical properties of polymer nanoparticles in many programs [78], including controlled drug delivery [31, 67, 77].

An electrokinetic microfluidic device for rapid, low-power drug delivery in self-sustaining microcontrollers evolved as a low-power, powerful, electrically active

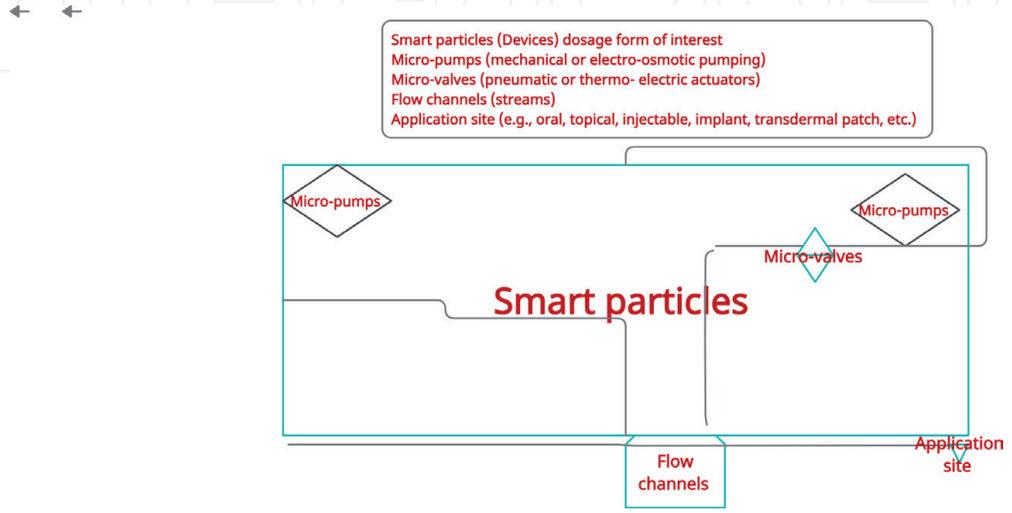

Figure 2.
Fluid-handling systems for the microfabrication of smart materials, including pumps, valves, and flow channels.

microwell intended for use in self-sustaining microcontrollers. The tool features a silicon primary base shape at the top that represents the drug storage location and PDMS (polydimethylsiloxane) that is electrically functionalized as a polymer. The drug release mechanism evolved here utilizes local electrokinetic results of controlled drug release times and compound velocities stored in appropriate, unbiased storage areas [79, 80]. This proves that the dose time can be reduced from hours to seconds over the preceding diffusion, primarily based on the use of low intensities of 20 mJ for the dose. Release techniques are completed in less than 2 minutes or with the use of low energy of 20 mJ. Each of these has an advantage over the state of the artwork subsystem [79]. A version of the electrokinetic delivery involved in the release technique used detailed 3D numerical simulations. The simulated model showed that a large part of the content is released by this technology at an early stage. It also provides a physical view of the delivery process [20, 79]. Such microfabrication is illustrated [81] in **Figure 2**.

4. Conclusions

In conclusion, microfluidic technology allows for incredibly accurate fluid delivery. It could be coupled to an actuator system that delivers drugs on demand or continuously. Microfluidics has revolutionized the design of devices for direct drug delivery in general, as well as the manufacturing of drug carriers. Microfluidic technology is required for the manufacture of drug carriers with a reproducible release profile as well as the controlled release of several substances with varied release characteristics. Materials with smart properties can be manipulated to respond in a controllable and reversible way, modifying some of their properties as a result of external stimuli such as mechanical stress or a certain temperature.

Conflict of interest

The author declares no conflict of interest.

Author details

Fikadu Ejeta
Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Medicine and Health Sciences, Mizan-Tepi University, Ethiopia

*Address all correspondence to: fikaduejeta@gmail.com

References

[1] Viseu A. Nanomedicine. Encyclopedia Britannica. 2020. Available from: https://www.britannica.com/science/nanomedicine. [Accessed: 31 July 2021]

[2] Farokhzad OC, Langer R. Impact of nanotechnology on drug delivery. ACS Nano. 2009;**3**(1):1-7. DOI: 10.1021/nn900002m

[3] Juliano R. Nanomedicine: Is the wave cresting? Nature Reviews. Drug Discovery. 2013;**12**(3):171-172. DOI: 10.1038/nrd3958

[4] Wagner V, Dullaart A, Bock AK, Zweck A. The emerging nanomedicine landscape. Nature Biotechnology. 2006;**24**(10):1211-1217. DOI: 10.1038/nbt1006-1211

[5] Park K. Facing the truth about nanotechnology in drug delivery. ACS Nano. 2013;**7**(9):7442-7447. DOI: 10.1021/nn404501g

[6] Tomeh MA, Zhao X. Recent advances in microfluidics for the preparation of drug and gene delivery systems. Molecular Pharmaceutics. 2020;**17**(12):4421-4434. DOI: 10.1021/acs.molpharmaceut.0c00913

[7] Riahi R, Tamayol A, Shaegh SAM, Ghaemmaghami AM, Dokmeci MR, Khademshosseini A. Microfluidics for advanced drug delivery systems. Current Opinion in Chemical Engineering. 2015;**7**:101-112. DOI: 10.1016/j.coche.2014.12.001

[8] Kwak B, Ozcelikkale A, Shin CS, Park K, Han B. Simulation of complex transport of nanoparticles around a tumor using tumor-microenvironment-on-chip. Journal of Controlled Release. 2014;**194**:157-167. DOI: 10.1016/j.jconrel.2014.08.027

[9] Shamsi M, Zahedi P, Ghourchian H, Minaeian S. Microfluidic-aided fabrication of nanoparticles blend based on chitosan for a transdermal multidrug delivery application. International Journal of Biological Macromolecules. 2017;**99**:433-442. DOI: 10.1016/j.ijbiomac.2017.03.013

[10] Ahn J, Ko J, Lee S, Yu J, Kim YT, Jeon NL. Microfluidics in nanoparticle drug delivery: From synthesis to pre-clinical screening. Advanced Drug Delivery Reviews. 2018;**128**:29-53. DOI: 10.1016/j.addr.2018.04.001

[11] Zhao X et al. Hierarchically porous composite microparticles from microfluidics for controllable drug delivery. Nanoscale. 2018;**10**(26):12595-12604. DOI: 10.1039/c8nr03728k

[12] Liu D, Zhang H, Fontana F, Hirvonen JT, Santos HA. Microfluidic-assisted fabrication of carriers for controlled drug delivery. Lab on a Chip. 2017;**17**(11):1856-1883. DOI: 10.1039/c7lc00242d

[13] Berkland C, King M, Cox A, Kim K, Pack DW. Precise control of PLG microsphere size provides enhanced control of drug release rate. Journal of Controlled Release. 2002;**82**(1):137-147. DOI: 10.1016/S0168-3659(02)00136-0

[14] Duncanson WJ, Lin T, Abate AR, Seiffert S, Shah RK, Weitz DA. Microfluidic synthesis of advanced microparticles for encapsulation and controlled release. Lab on a Chip. 2012;**12**(12):2135-2145. DOI: 10.1039/c2lc21164e

[15] Araújo F et al. Microfluidic assembly of a multifunctional tailorable composite system designed for site specific

combined oral delivery of peptide drugs. ACS Nano. 2015;**9**(8):8291-8302. DOI: 10.1021/acsnano.5b02762

[16] Stuart MAC et al. Emerging applications of stimuli-responsive polymer materials. Nature Materials. 2010;**9**(2):101-113. DOI: 10.1038/nmat2614

[17] Zhao CX. Multiphase flow microfluidics for the production of single or multiple emulsions for drug delivery. Advanced Drug Delivery Reviews. 2013;**65**(11-12):1420-1446. DOI: 10.1016/j.addr.2013.05.009

[18] Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. Nature Materials. 2013;**12**(11):991-1003. DOI: 10.1038/nmat3776

[19] Huang X et al. Microfluidic hydrodynamic focusing synthesis of polymer-lipid nanoparticles for siRNA delivery. Oncotarget. 2017;**8**(57):96826-96836. DOI: 10.18632/oncotarget.18281

[20] Lin YS et al. Microfluidic synthesis of microfibers for magnetic-responsive controlled drug release and cell culture. PLoS One. 2012;**7**(3):4-11. DOI: 10.1371/journal.pone.0033184

[21] Karnik R et al. Microfluidic platform for controlled synthesis of polymeric nanoparticles. Nano Letters. 2008;**8**(9):60-75

[22] Tahir N et al. Microfluidic fabrication and characterization of Sorafenib-loaded lipid-polymer hybrid nanoparticles for controlled drug delivery. International Journal of Pharmaceutics. 2020;**581**(March):119275. DOI: 10.1016/j.ijpharm.2020.119275

[23] Tasci ME et al. Production, optimization and characterization of polylactic acid microparticles using electrospray with porous structure. Applied Sciences. 2021;**11**(11):1-13. DOI: 10.3390/app11115090

[24] Fantini D, Zanetti M, Costa L. Polystyrene microspheres and nanospheres produced by electrospray. Macromolecular Rapid Communications. 2006;**27**(23):2038-2042. DOI: 10.1002/marc.200600532

[25] Xu Y, Hanna MA. Electrospray encapsulation of water-soluble protein with polylactide: Effects of formulations on morphology, encapsulation efficiency and release profile of particles. International Journal of Pharmaceutics. 2006;**320**(1):30-36. DOI: 10.1016/j.ijpharm.2006.03.046

[26] Hennequin Y et al. Synthesizing microcapsules with controlled geometrical and mechanical properties with microfluidic double emulsion technology. Langmuir. 2009;**25**(14):7857-7861. DOI: 10.1021/la9004449

[27] Whitesides GM. The origins and the future of microfluidics. Nature. 2006;**442**(7101):368-373. DOI: 10.1038/nature05058

[28] Tokeshi M, Sato K. Micro/nano devices for chemical analysis. Micromachines. 2016;**7**(9):6-8. DOI: 10.3390/mi7090164

[29] Huh D, Matthews BD, Mammoto A, Montoya-Zavala M, Hsin HY, Ingber DE. Reconstituting organ-level lung functions on a chip. Science (80-). 2010;**328**(5986):1662-1668. DOI: 10.1126/science.1188302

[30] Bhise NS et al. Organ-on-a-chip platforms for studying drug delivery systems. Journal of Controlled Release. 2014;**190**:82-93. DOI: 10.1016/j.jconrel.2014.05.004

[31] Thorsen T, Roberts RW, Arnold FH, Quake SR. Dynamic pattern formation in a vesicle-generating microfluidic device. Physical Review Letters. 2001;**86**(18):4163-4166. DOI: 10.1103/PhysRevLett.86.4163

[32] Nisisako T, Torii T, Higuchi T. Droplet formation in a microchannel network. Lab on a Chip. 2002;**2**(1):24-26. DOI: 10.1039/b108740c

[33] Kim JW, Fernández-Nieves A, Dan N, Utada AS, Marquez M, and Weitz DA. "Colloidal assembly route for responsive colloidosomes with tunable permeability," Nano Letters. 2007;**7**(9):2876-2880. DOI: 10.1021/nl0715948

[34] De Geest BG, Urbanski JP, Thorsen T, Demeester J, and De Smedt SC. "Synthesis of monodisperse biodegradable microgels in microfluidic devices," Langmuir. 2005;**21**(23):10275-10279. DOI: 10.1021/la051527y

[35] Tan WH, Takeuchi S. Monodisperse alginate hydrogel microbeads for cell encapsulation. Advanced Materials. 2007;**19**(18):2696-2701. DOI: 10.1002/adma.200700433

[36] Clausell-Tormos J et al. Droplet-based microfluidic platforms for the encapsulation and screening of mammalian cells and multicellular organisms. Chemistry & Biology. 2008;**15**(5):427-437. DOI: 10.1016/j.chembiol.2008.04.004

[37] Chang J-Y, Yang C-H, Huang K-S. Microfluidic assisted preparation of CdSe/ZnS nanocrystals encapsulated into poly(DL-lactide-co-glycolide) microcapsules. Nanotechnology. 2007;**18**(30):305305. DOI: 10.1088/0957-4484/18/30/305305

[38] Zhao X, Bian F, Sun L, Cai L, Li L, Zhao Y. Microfluidic generation of nanomaterials for biomedical applications. Small. 2020;**16**(9):1-19. DOI: 10.1002/smll.201901943

[39] Herranz-Blanco B, Ginestar E, Zhang H, Hirvonen J, Santos HA. Microfluidics platform for glass capillaries and its application in droplet and nanoparticle fabrication. International Journal of Pharmaceutics. 2017;**516**(1-2):100-105. DOI: 10.1016/j.ijpharm.2016.11.024

[40] J. Pessi, H. A. Santos, I. Miroshnyk, Joukoyliruusi, D. A. Weitz, and S. Mirza, "Microfluidics-assisted engineering of polymeric microcapsules with high encapsulation efficiency for protein drug delivery," International Journal of Pharmaceutics. 2014;**472**(1-2):82-87. DOI: 10.1016/j. ijpharm.2014.06.012

[41] Olanrewaju A, Beaugrand M, Yafia M, Juncker D. Capillary microfluidics in microchannels: From microfluidic networks to capillaric circuits. Lab on a Chip. 2018;**18**(16):2323-2347. DOI: 10.1039/c8lc00458g

[42] Martins JP, Torrieri G, Santos HA. The importance of microfluidics for the preparation of nanoparticles as advanced drug delivery systems. Expert Opinion on Drug Delivery. 2018;**15**(5):469-479. DOI: 10.1080/17425247.2018.1446936

[43] Gale BK et al. A review of current methods in microfluidic device fabrication and future commercialization prospects. Inventions. 2018;**3**(3):60-75. DOI: 10.3390/inventions3030060

[44] Niculescu AG, Chircov C, Bîrcă AC, Grumezescu AM. Fabrication and applications of microfluidic devices: A review. International Journal of

Molecular Sciences. 2021;**22**(4):1-26. DOI: 10.3390/ijms22042011

[45] Chiesa E et al. The microfluidic technique and the manufacturing of polysaccharide nanoparticles. Pharmaceutics. 2018;**10**(4):267-290. DOI: 10.3390/pharmaceutics10040267

[46] Caldorera-Moore M, Guimard N, Shi L, Roy K. Designer nanoparticles: Incorporating size, shape and triggered release into nanoscale drug carriers. Expert Opinion on Drug Delivery. 2010;**7**(4):479-495. DOI: 10.1517/17425240903579971

[47] R. C. S. Bicudo and M. H. A. Santana, "Production of hyaluronic acid (HA) nanoparticles by a continuous process inside microchannels: Effects of non-solvents, organic phase flow rate, and HA concentration," Chemical Engineering Science. 2012;**84**:134-141.DOI: 10.1016/j.ces.2012.08.010

[48] Arduino I et al. Preparation of cetyl palmitate-based PEGylated solid lipid nanoparticles by microfluidic technique. Acta Biomaterialia. 2021;**121**(xxxx):566-578. DOI: 10.1016/j.actbio.2020.12.024

[49] Damiati S, Kompella UB, Damiati SA, Kodzius R. Microfluidic devices for drug delivery systems and drug screening. Genes (Basel). 2018;**9**(2):103-127. DOI: 10.3390/genes9020103

[50] Laity P, Cassidy A, Skepper J, Jones B, Cameron R. Investigation into the intragranular structures of microcrystalline cellulose and pre-gelatinised starch. European Journal of Pharmaceutics and Biopharmaceutics. 2010;**74**(2):377-387. DOI: 10.1016/j.ejpb.2009.10.006

[51] Coluccio ML et al. Microfluidic platforms for cell cultures and investigations. Microelectronic Engineering. 2019;**208**(January):14-28. DOI: 10.1016/j.mee.2019.01.004

[52] Grüll H, Langereis S. Hyperthermia-triggered drug delivery from temperature-sensitive liposomes using MRI-guided high intensity focused ultrasound. Journal of Controlled Release. 2012;**161**(2):317-327. DOI: 10.1016/j.jconrel.2012.04.041

[53] Kim HJ, Huh D, Hamilton G, Ingber DE. Human gut-on-a-chip inhabited by microbial flora that experiences intestinal peristalsis-like motions and flow. Lab on a Chip. 2012;**12**(12):2165-2174. DOI: 10.1039/c2lc40074j

[54] Le TN, Nguyen VA, Bach GL, Tran LD, Cao HH. Design and fabrication of a PDMS-based manual micro-valve system for microfluidic applications. Advances in Polymer Technology. 2020;**2020**:1-8. DOI: 10.1155/2020/2460212

[55] Khan IU, Serra CA, Anton N, Vandamme TF. Production of nanoparticle drug delivery systems with microfluidics tools. Expert Opinion on Drug Delivery. 2015;**12**(4):547-562. DOI: 10.1517/17425247.2015.974547

[56] Kim DY, Jin SH, Jeong SG, Lee B, Kang KK, Lee CS. Microfluidic preparation of monodisperse polymeric microspheres coated with silica nanoparticles. Scientific Reports. 2018;**8**(1):1-11. DOI: 10.1038/s41598-018-26829-z

[57] Zhou W, Feng M, Valadez A, Li XJ. One-step surface modification to graft dna codes on paper: The method, mechanism, and its application. Analytical Chemistry. 2020;**92**(10):7045-7053. DOI: 10.1021/acs.analchem.0c00317

[58] Trouillon R, Gijs MAM. Dynamic electrochemical quantitation of dopamine release from a cells-on-paper system. RSC Advances. 2016;**6**(37):31069-31073. DOI: 10.1039/c6ra02487d

[59] Mao K et al. Paper-based microfluidics for rapid diagnostics and drug delivery. Journal of Controlled Release. 2020;**322**(March):187-199. DOI: 10.1016/j.jconrel.2020.03.010

[60] Huang KS, Yang CH, Wang YC, Wang WT, Lu YY. Microfluidic synthesis of vinblastine-loaded multifunctional particles for magnetically responsive controlled drug release. Pharmaceutics. 2019;**11**(5);212-226. DOI: 10.3390/pharmaceutics11050212

[61] Liu D et al. Microfluidic assembly of monodisperse multistage pH-responsive polymer/porous silicon composites for precisely controlled multi-drug delivery. Small. 2014;**10**(10):2029-2038. DOI: 10.1002/smll.201303740

[62] Amoyav B, Benny O. Microfluidic based fabrication and characterization of highly porous polymeric microspheres. Polymers (Basel). 2019;**11**:419. DOI: 10.3390/polym11030419

[63] Vasiliauskas R et al. Simple microfluidic approach to fabricate monodisperse hollow microparticles for multidrug delivery. ACS Applied Materials & Interfaces. 2015;**7**(27):14822-14832. DOI: 10.1021/acsami.5b04824

[64] Zhang L, Chen Q, Ma Y, Sun J. Microfluidic methods for fabrication and engineering of nanoparticle drug delivery systems. ACS Applied Bio Materials. 2019;**3**(1):107-120. DOI: 10.1021/acsabm.9b00853

[65] Xu Q et al. Preparation of monodisperse biodegradable polymer microparticles using a microfluidic flow-focusing device for controlled drug delivery. Small. 2009;**5**(13):1575-1581. DOI: 10.1002/smll.200801855

[66] Maher S et al. Multifunctional microspherical magnetic and pH responsive carriers for combination anticancer therapy engineered by droplet-based microfluidics. Journal of Materials Chemistry B. 2017;**5**(22):4097-4109. DOI: 10.1039/c7tb00588a

[67] Dashtimoghadam E, Mirzadeh H, Taromi FA, Nyström B. Microfluidic self-assembly of polymeric nanoparticles with tunable compactness for controlled drug delivery. Polymer (Guildf). 2013;**54**(18):4972-4979. DOI: 10.1016/j.polymer.2013.07.022

[68] Mu X, Gan S, Wang Y, Li H, Zhou G. Stimulus-responsive vesicular polymer nano-integrators for drug and gene delivery. International Journal of Nanomedicine. 2019;**14**:5415-5434. DOI: 10.2147/IJN.S203555

[69] Chen W, Meng F, Cheng R, Zhong Z. pH-Sensitive degradable polymersomes for triggered release of anticancer drugs: A comparative study with micelles. Journal of Controlled Release. 2010;**142**(1):40-46. DOI: 10.1016/j.jconrel.2009.09.023

[70] Paasonen L, Laaksonen T, Johans C, Yliperttula M, Kontturi K, Urtti A. Gold nanoparticles enable selective light-induced contents release from liposomes. Journal of Controlled Release. 2007;**122**(1):86-93. DOI: 10.1016/j.jconrel.2007.06.009

[71] Ganta S, Devalapally H, Shahiwala A, Amiji M. A review of stimuli-responsive nanocarriers for drug and gene delivery. Journal of Controlled Release. 2008;**126**(3):187-204. DOI: 10.1016/j.jconrel.2007.12.017

[72] Ranjan A et al. Image-guided drug delivery with magnetic resonance guided high intensity focused ultrasound and temperature sensitive liposomes in a rabbit Vx2 tumor model. Journal of Controlled Release. 2012;**158**(3):487-494. DOI: 10.1016/j.jconrel.2011.12.011

[73] Meng L, Deng Z, Niu L, Cai F, Zheng H. Controlled thermal-sensitive liposomes release on a disposable microfluidic device. Proceedings Under Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). 2015;**2015**(November):5912-5915. DOI: 10.1109/EMBC.2015.7319737

[74] Meng L et al. A disposable microfluidic device for controlled drug release from thermal-sensitive liposomes by high intensity focused ultrasound. Theranostics. 2015;**5**(11):1203-1213. DOI: 10.7150/thno.12295

[75] Liu D et al. "Core/Shell Nanocomposites Produced by Superfast Sequential Microfluidic Nanoprecipitation." Nano Letters. 2017

[76] Morikawa Y, Tagami T, Hoshikawa A, Ozeki T. The use of an efficient microfluidic mixing system for generating stabilized polymeric nanoparticles for controlled drug release. Biological & Pharmaceutical Bulletin. 2018;**41**(6):899-907. DOI: 10.1248/bpb.b17-01036

[77] Wang J et al. A microfluidic tubing method and its application for controlled synthesis of polymeric nanoparticles. Lab on a Chip. 2014;**14**(10):1673-1677. DOI: 10.1039/c4lc00080c

[78] Bazban-Shotorbani S, Dashtimoghadam E, Karkhaneh A, Hasani-Sadrabadi MM, Jacob KI. Microfluidic directed synthesis of alginate nanogels with tunable pore size for efficient protein delivery. Langmuir. 2016;**32**(19):4996-5003. DOI: 10.1021/acs.langmuir.5b04645

[79] Chung AJ, And DK, Erickson D. Electrokinetic microfluidic devices for rapid, low power drug delivery in autonomous microsystems. Lab on a Chip. 2008;**8**(2):330-338. DOI: 10.1039/b713325a

[80] Santini JT, Richards AC, Scheidt R, Cima MJ, Langer R. Microchips as controlled drug-delivery devices. Angewandte Chemie, International Edition. 2000;**39**(14):2396-2407. DOI: 10.1002/1521-3773(20000717)39:14<2396::AID-ANIE2396>3.0.CO;2-U

[81] Ejeta F. Recent advances of microfluidic platforms for controlled drug delivery in nanomedicine. Drug Design, Development and Therapy. 2021;**15**:3881-3891. DOI: 10.2147/DDDT.S324580