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2021

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The final publication is available at:
Forigua, A., Kirsch, R. L., Willerth, S. M., & Elvira, K. S. (2021). Recent advances in the design of microfluidic technologies for the manufacture of drug releasing particles. *Journal of Controlled Release*, *333*, 258–268. https://doi.org/10.1016/j.jconrel.2021.03.019

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Recent advances in the design of microfluidic technologies for the manufacture of drug releasing particles

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Abstract

Drug releasing particles are valued for their ability to deliver therapeutics to targeted locations and for their controllable release patterns. The development of microfluidic technologies, which are designed specifically to manipulate small amounts of fluids, to manufacture particles for drug delivery applications reflects a recent trend due to the advantages they confer in terms of control over particle size and material composition. This review takes a comprehensive look at the different types of microfluidic devices used to fabricate such particles from different types of biomaterials, and at how the on-chip features enable the production of particles with different types of properties. The review concludes by suggesting avenues for future work that will enable these technologies to fulfill their potential and be used in industrial settings for the manufacture of drug releasing particles with unique capabilities.

Keywords: microfluidics, drug release, microparticles, nanoparticles, droplets

1. Introduction

Microfluidic technologies control and manipulate fluids at the micron scale, usually in a network of channels that have been molded or etched into a material such as plastic or glass. These technologies have been available since 1975 but were not widely used until the 1990s [1], when they became popular for applications such as DNA sequencing, biological detection, and polymerase chain reaction amplification [2]. In the early 21st century, microfluidic technologies started to be used to create “organs-on-a-chip" with living cells that act as organ tissues and can be used to evaluate drugs [2,3]. Microfluidic technologies also have many applications outside the field of healthcare, such as the stabilization of food products [4], ensuring food safely [5,6], biosensing [7], agriculture [8] and cell culture [9]. This review focuses on microfluidic platforms used to manufacture drug releasing particles published within the last five years, and the advantages that these technologies confer in terms of allowing these particles to be produced with distinct properties and compositions [10]. Specifically, how the microfluidic devices are fabricated, the advantages and disadvantages of the different materials used for device fabrication, and the on-chip architectures and features used to create drug releasing particles from different types of biomaterials are discussed. The review concludes by describing several areas where further research will enable these technologies to reach their full potential.

1.1. Formulating drug releasing particles

Drug releasing particles deliver a therapeutic agent to a certain site at a specific time based on the method of fabrication and the properties of the material used for encapsulation along with the agent being delivered. Hence, there has been extensive research in this area due to their increasing importance in the fields of biotechnology and medicine [11–13]. Drug releasing particles can achieve targeted delivery because their small size allows them to penetrate cell membranes, bind and stabilize proteins and escape via lysosomes during degradation [14]. Site specific delivery minimizes the side effects that would be caused by other therapies. Along with release at specific sites, these particles show prolonged delivery compared to other methods [15]. For example, these particles can be delivered to specific cells or molecules in the body, such as targeting tumors [16], or can be used to deliver drugs across the blood-brain barrier which is one of the most restrictive barriers for drug access in the body, due to their small size, nontoxicity, and prolonged blood circulation [17–19]. The type of biomaterial used to fabricate these particles along with their target

cargo determine their properties, including particle size and release rate [20]. The properties discussed in this section are not intrinsic properties of these particles since the particles must be designed specifically for their desired functionality in terms of delivery rate and concentration.

The are many types of particles used for drug delivery that can be broadly divided into nano and microparticles. Microparticles are the largest category, with microcapsules and microspheres being subsets within it [21]. Microcapsule is an inclusive term that defines particles with a membrane shell surrounding a core, whereas microspheres refer to particles where the active drug is dispersed throughout [11]. Microparticles can also be further divided into solid, core-shell, and multicompartmental microparticles. These different types of particles allow for various individual properties, applications, and advantages/disadvantages for their use as drug releasing agents. Solid microparticles include spherical, non-spherical, homogeneous and heterogeneous structures. Core-shell particles are made from two components, a shell and a core, that together give the particle enhanced characteristics compared to the singular components. On the nanoscale, there are many different types of nanoparticle systems available for drug delivery. These systems include nanoparticles themselves, which can be solid or hollow, and can be polymeric, or inorganic, such as magnetic nanoparticles [22–24]. Lipid nanoparticles can be solid, nanostructured lipid carriers, or lipid drug conjugates [23]. Furthermore, among this scale of particle, there are also liposomes, dendrimers, nanocrystals, and nanotubes [25–28]. Finally, Janus particles are another type of drug releasing particle that contain two asymmetric regions, each made of different compositions [29].

The composition of drug releasing particles plays an important role in their release profile. The main characteristics to consider when choosing particle material include biodegradability, non-toxicity, and biocompatibility. Other factors include the drug release profile, properties of the drug, size of the particle wanted, and surface characteristics such as charge or permeability. Drug releasing particles are commonly made from polymers, lipids, proteins, magnetic materials and other types of inorganic materials. Each material has different advantages and disadvantages. Polymeric materials possess low toxicity, are typically stable, and can be altered to the physiological environment they are designed for [30]. Polymer materials can be classified broadly as natural and synthetic. Popular synthetic polymers include polylactide (PLA), poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), and polycaprolactone (PCL). Natural polymers include chitosan, gelatin, sodium alginate and albumin. Inorganic particles can include those made

of silver, gold, iron, oxide, and silica. Particles made from proteins have good biocompatibility, biodegradability, and ability for surface modification [31]. These particles are commonly made from proteins such as albumin, gelatin, and elastin.

1.2. The fundamentals of microfluidics

Various forces, such as inertia and capillarity, act on fluids in microfluidic systems and affect the flow regimes through the microchannels within a microfluidic device. Fluid flow can be generally described as turbulent or laminar. Only laminar flow typically occurs in microfluidic systems due to the micro-scale size of the device features. This means the flow patterns in microfluidic devices are very different to those found in macro systems. These physical parameters are important to consider when designing and operating microfluidic devices for the formation of drug releasing particles. A common example is that due to laminar flow, mixing only happens through diffusion in microfluidic devices, which means that if rapid mixing of fluids is required, mixing components need to be integrated into the device design.

Droplet-based microfluidic technologies are commonly used to produce drug releasing particles. In this type of microfluidic platform, two immiscible phases, a continuous (usually oil) and a dispersed phase (usually water), are brought together to generate an emulsion (usually water-in-oil droplets) that can be used to produce drug releasing particles. Droplet-based microfluidic technologies also allow the creation of double or multiple emulsions, where these initial droplets are encapsulated into further non-miscible fluids to create, for example, water-in-oil-in-water double emulsions. These emulsions can then be used as templates to make particles with complex compositions. Surface tension, interfacial forces and viscosity are some of the physical parameters that affect microfluidic droplet formation [32]. The interplay between these forces will determine whether droplets are created via a dripping mode, where the droplets are formed at the droplet generator, or whether droplets will be created through a jetting mode, where a continuous stream is broken up into droplets further down the microchannel. Flow rate also affects droplet production, and altering this will change the size of particles being produced [33].

Droplets can be created on microfluidic devices using passive or active methods. Passive microfluidic devices do not require any additional energy input because they create droplets through forces generated by the fluids themselves [34]. Dripping and jetting are both considered passive droplet generation (along with squeezing, tip-streaming, and tip-multi-breaking). On the

other hand, active generation of droplets involves the use of an external energy input (such as electrical valves, centrifugal forces, and magnetic beads) to form droplets [32]. Active microfluidic devices allow for the creation of more complex particles, but can cause challenges because device fabrication tends to be more difficult, and miniaturization of the overall platform is also harder since it is not straightforward to miniaturize the components required for active droplet generation such as valves and external micromixers [35,36].

1.3. Advantages and disadvantages of microfluidic technologies for the formation of drug releasing particles

Microfluidic technologies can be employed to produce drug releasing particles with a variety of compositions and capabilities, with this method showing many advantages over conventional production methods [37]. An important advantage is that microfluidic methods result in particles smaller in size and with greater uniformity than those made with batch or semi-batch systems [33]. This is important as particles of different sizes are absorbed differently in the body and, when releasing drugs, the particles typically need to be absorbed in a specific region to obtain their intended effect. Another advantage is that only small amounts of reagents need to be used: approximately 100-1000 times less than the amount used in other methods [38]. Moreover, microfluidic technologies allow for easy control over the size of particles produced by manipulating the flow rate of the fluid phases [39], increase drug encapsulation efficiency and the drug loading level [40], and they can also easily be used to make a library of particles with different compositions and properties [41]. Particles created with microfluidic technologies can be made with advanced qualities such as double compartments, pH responsiveness and controlled release [42,43]. Conventional bulk methods to make drug releasing particles cannot be used to make particles with controlled qualities such as size and structure [44].

One major disadvantage of using microfluidic technologies for the manufacture of drug releasing particles is the large amount of time needed to produce significant amounts of the particles due to typical droplet production rates being only 0.1-10 mL/h from a single droplet generator [45]. Due to this, drug releasing particles produced by microfluidic technologies are not yet widely used in industrial applications [46]. The low production rates can be combated by using multiple devices in parallel (parallelization) for increased production, but this technology is still relatively new.

1.4. Non-microfluidic methods for the formation of drug releasing particles

The use of microfluidic technologies to make drug releasing particles is relatively new, and there are many other systems that can produce these types of particles. Some of the most commonly used batch or semi-batch methodologies are presented here:

Batch stirring is a traditional and simple method of drug releasing particle production. This method begins with an initial phase to which a drug/matrix dispersion is added during continuous mixing to form drug releasing particles [47]. The second mixture can be added either in a dropwise fashion or all at once. Studies have compared this traditional method to new microfluidic methods, outlining the advantages and disadvantages of each process, and while batch stirring has high production rates, it typically lacks control over particle size and uniformity [7]. PCL, PLGA and ethyl cellulose (EC) are some of the examples of the polymeric biomaterials that have been used for the fabrication of drug releasing particles using batch stirring [48]. This technique can also be used for the formation of particles from natural biomaterials such as proteins and lipid extracts [49,50].

Emulsification is another common method used to produce drug releasing particles. Different types of emulsions can be formed, such as oil/water (o/w) or water/oil (w/o) emulsions, double water/oil/water (w/o/w) emulsions and oil/oil (o/o) emulsions [51–53]. The oil phase is added to a continuous aqueous phase containing a stabilizing molecule (emulsifier) to form drug releasing particles using a single o/w emulsion. Preparation of w/o emulsions occurs in the opposite manner, with the aqueous phase being added to the continuous oil phase [52]. Double w/o/w emulsion formation occurs when a drug solution is added into a polymeric organic phase to make a primary emulsion, which is then added to an aqueous solution in the presence of another polymer (to make the secondary emulsion). Finally, o/o emulsions are prepared by adding one oil phase to another immiscible oil containing an emulsifier [54]. Emulsification has been used for the formation of particle matrices made from block copolymers such as PCL, PLGA, PLA, poly(vinylpyrrolidone), and polyurethane; natural fibres such as alginate, and can be used to form Pickering emulsions, where the emulsifier is a solid, such as silica [52–56].

Solvent evaporation produces drug releasing particles using various types of emulsions and polymers. The polymer material is first dissolved in a volatile organic solvent during the emulsification process [48]. Then, the drug is dissolved in an organic solvent to make a solution,

suspension, or emulsion [48]. Next, the organic phase (including the drug) is emulsified with the polymers. Finally, the organic solvent is evaporated (for example by using agitation), resulting in a hardened particle [48,57]. As this technique relies on the volatility of solvents, biomaterials need to be soluble in organic solvents with low vapor pressures. Therefore, the possibilities range from PCL, PLGA and PLA as block copolymers, to the use of small molecules such as proteins, nanofibers and hydrogels [48,57].

Phase separation is a technique used to make drug releasing particles in three basic steps in an aqueous system [58]. The steps involved in this process include forming three phases, then dispersing the core material into an immiscible polymer solution, and finally coating the core material. All phases are completed during continuous mixing. This technique is generally used to create particles with extended release of hydrophilic drugs. Such drugs require the use a highly polar solvent system to reach efficient microencapsulation. Some of the biomaterials compatible with highly polar dispersed phases used in phase separation to make particles include biopolymers such as EC, cellulose acetate butyrate, and Eudragit RS/RL [58].

Nanoprecipitation (also known as the solvent displacement method), a commonly used method of creating nanoparticles, requires the use of two miscible solvents [59]. In this method a polymer and a drug are dissolved together (solvent solution), and then added in a dropwise fashion to a second solution (non-solvent) while the mixture is stirred [60]. The polymer immediately precipitates once added to the non-solvent, resulting in instantaneous particle formation [59]. This method is common for the fabrication of nanoparticles with a biodegradable polymer matrix made from materials such as PLA, PLGA, and poly(cyanoacrylate) [60].

Polymerization can also be used to produce drug releasing particles. There are two main types of polymerization methods used to produce microparticles: one starting from an initiator and a monomer, and another from a linear polymer chain [20]. Polymerization then occurs, making drug releasing particles form instantaneously [61]. This technique is commonly used for the production of micro and nanoparticles from biomaterials such as polyester based copolymers [20].

Spray drying is a less common, but simple method for creating drug releasing particles [62]. This method consists of four main steps: liquid atomization, blending the fluid with a drying gas, fluid dissipation, and partitioning of dried particles from the gas [48]. This is a continuous process, and the batch size can be controlled easily so large-scale production of drug releasing particles is a

feasible option with this method [63]. Spray drying is compatible with the fabrication of micro and nanoparticles for drug delivery using biomaterials such as EC, cyclodextrin, chitosan, PLA and lipids such as dipalmitoylphosphatidylcholine (DPPC) [48].

Supercritical fluids can produce drug releasing particles by using a condensed gas which acts as a solvent to precipitate the solute. This solution is then expanded through a nozzle to depressurize it, resulting in a sharp drop in solute solubility and hence solute supersaturation occurs that causes its precipitations [64]. In other words, particle formation results from the rapid expansion of the supercritical fluid. There are many variations on the basic technique depending on the type of materials used. The added solubility caused by the supercritical fluids allows for the formation of particles made from large block copolymers, which are usually derived polyesters [64]. In addition, this technique is capable of forming aerogels and hydrogels for drug delivery using natural polymers such as gelatin, agar, cellulose, and alginates [64].

Self-healing encapsulation occurs spontaneously and typically requires three steps. First, drug free particles with pores are created. Next, the particles are placed in an aqueous drug solution allowing the drugs to enter the particles. Lastly, initiation of the "self-healing" process closes the pores, encapsulating the drug inside the particles. This method can include active or passive loading of drugs into the already constructed particles [65,66]. This technique is usually coupled with other techniques for particle formation in order to encapsulate the self-healing catalyzed fraction into the matrix as a precursor to particle formation. This is usually accomplished by mixing trace amounts of urea or melamine resins with biopolymers such as PLGA [66].

Extrusion for drug releasing particle production occurs by forcing the starting materials through an opening such as a nozzle [61]. This method offers small size distribution of particles, but also may cause damage to the therapeutic agent as you must force it through a small opening [61]. This method is commonly used in the formation of lipid particles in the form of liposomes [67].

Finally, the **fluidized bed coating and encapsulation method** takes place within a fluidized bed, where the therapeutic agent is fluidized with vertical air flow, while a liquid coating (a melt, suspension or solution) is sprayed onto the fluidized particles, encapsulating the agent [68,69]. Similarly to the self-healing technique, this method is usually coupled with other particle formation techniques, as the final step for the inclusion of drug material into the particles [69].

2. Design features of microfluidic devices for particle formation

The basic design of a microfluidic platform consists of a small, flat device with inlets and an outlet. The device houses the various microchannels for fluids to flow through and the features required to manipulate these fluids to form drug releasing particles. The fabrication of drug releasing particles on microfluidic platforms is usually performed using segmented flow (droplets). To form an emulsion on the microfluidic device, there is a junction at which the channels that carry each phase converge, which is designed to allow the fluids to meet in a manner which results in emulsion (droplet) formation. Segmented flow devices use specific channel geometries (T-junctions, flow-focusing junctions, etc.) to produce particles. Figure 1 illustrates these core designs. In order to be able to form drug releasing particles using microfluidic technologies, these device features must be assessed for compatibility with the type of particle that needs to be produced in terms of particle size and composition. The following section will discuss the most common features that are used in the fabrication of drug releasing particles using microfluidic technologies, their advantages and disadvantages and some of the latest published work.

2.1 Droplet formation at flow focusing geometries

The most common design used for droplet formation for drug releasing particle production are flow focusing junctions [70]. In this geometry the continuous phase squeezes the dispersed phase from the top and bottom at a cross-like junction, increasing the shear stress on the inner (droplet) phase and hence forming droplets. There are 2D and 3D flow focusing geometries, but the former are more common because they are simpler fabricate [71]. A flow focusing design enables the adjustment of the angle at which the phases meet, allowing the use of a wide variety of fluids, and creating emulsions even when there are significant differences in viscosity [70]. As a result, flow focusing geometries are the most frequently used droplet formation strategy for drug releasing particles because they confer advantages in the control of droplet size, consistency and rate of formation [70,72]. A wide variety of biomaterials can be used for the fabrication of drug releasing particles. These range from materials such as copolymers like PLGA, PEG, PCL and ethylene oxide to biological materials such as liposomes, polymer-DNA and polymer-lipid nano composites. Along with organic materials, organic fibers such as alginates, chitosan, polyurethane, poly(methyl methacrylate) (PMMA), and others have been used as the matrix for the fabrication of drug releasing particles in flow focusing junctions [72].

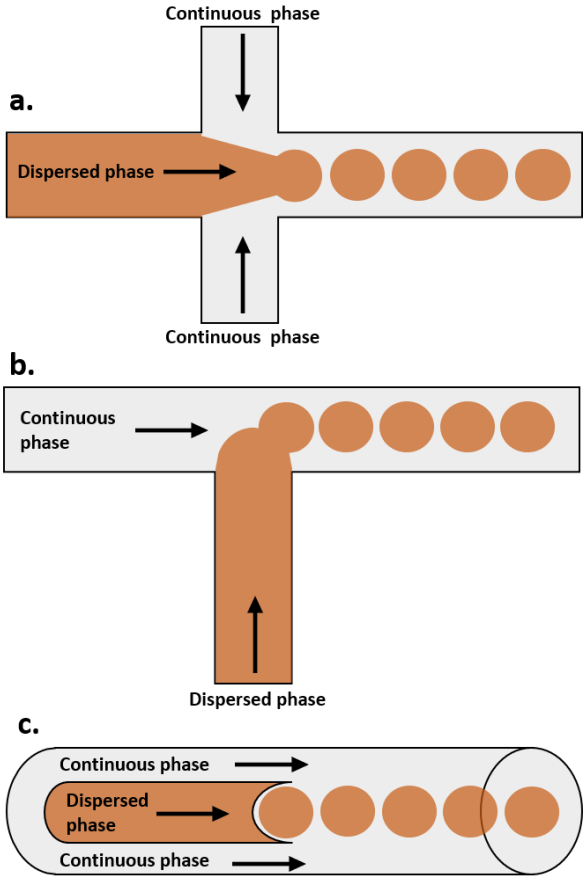

Figure 1. Most common designs used to make droplets in microfluidic devices. a) Droplet formation at a flow focusing junction. The two phases meet at a cross-like junction, where the continuous phase pinches off droplets of the dispersed phase from above and below. **b)** Droplet formation at a T-junction, where both phases meet at a t-shaped junction and the shear stress created by the continuous phase causes droplet formation. **c)** Droplet formation using a coaxial geometry, where the continuous phases completely surround the dispersed phase in three dimensions to create droplets.

The design of the flow focusing geometry affects droplet size, which may hence affect drug releasing particle size. The work done by Bashir *et al.* for a w/o system suggests that the droplet size is directly proportional to the angle at which the phases meet [73]. Their work reveals that on a hydrophobic microfluidic device where the continuous phase is oil and the dispersed phase is aqueous, the largest droplet diameter is achieved when the channels meet at 90°. However, the system was only tested using a dripping regime, where the droplets are generated at the junction, and not after the junction (downstream). The flow regime also plays an important role in the droplet size formed at flow focusing junctions. Anna *et al.* determined that the geometry (junction angles, channel dimensions, etc.) at which droplets are formed on a flow focusing junction affects the droplet formation regime [74]. When a system forms droplets close to the junction (dripping regime) at low capillary number (Ca), the droplet sizes are highly affected by the geometry of the junction. However, at high Ca, jetting or threading regimes are commonly established. Here the droplet sizes are less dependent on the junction geometry, and more dependent on the flow rate ratios between the phases. Hence, it is important to consider the relative viscosity (i.e., Ca) of the phases used for the formation of drug releasing particles.

Some recent salient examples of flow focusing geometries used for the formation of drug releasing particles are presented here. Kwon *et al.* produced drug releasing particles of sizes between 25 and 160 μm, with a coefficient of variation (CV) of less than 5% using a glass microfluidic device with a flow focusing junction at a 70° [33]. To achieve this, the flow regimes were varied from a threading regime at high flow rate ratios to create the smaller sized particles, to a dripping regime where the larger particles were formed. Park *et al.* fabricated PCL microspheres with adjustable porosity using a polydimethylsiloxane (PDMS) microfluidic device with a flow focusing junction at a 45° angle [75]. The porosity was created and controlled by the addition of camphene and ramping of temperatures for the release of the volatile molecule [75]. Morita *et al.* formed drug releasing particles from another biodegradable polymer (PLGA), using a glass microfluidic device with a flow focusing junction at a 90° angle to form particles of consistent sizes which enclosed a water insoluble drug [76].

Flow focusing geometries allow the easy formation of multiple emulsions, enabling the formation of drug releasing particles with enhanced functionalities. Amoyav *et al.* used a flow focusing junction for the formation of multiple emulsions, and show that by changing the concentration of

biopolymer present in the oil phase (PLGA or PLA) it is possible to form porous microspheres [77]. Flow focusing junctions can also be used to form drug releasing particles using more than one material. Kim *et al.* developed a protocol in which poly (1,10-decanediol dimethacrylate-co-trimethoxysillyl propyl methacrylate) hybrid microspheres were fabricated using droplet microfluidics and the polymers were photoactivated *in situ* [78]. Dong *et al.* developed a mixed organic/inorganic system (PGLA/TiO_2) in which hydrolyzation of then metallic oxide was achieved *in situ,* yielding a corrugated surface [79]. Magnetic drug releasing particles composed of magnetite coated with polyethylene oxide nitrodopamine were synthesized and characterized by Häfeli *et al.* using a similar system in which a magnetic material is suspended in the dispersed phase [80,81]. Due to the complexity of these drug releasing particles, control over the droplet size and composition is critical, and hence the use of a flow focusing junction is necessary to enable optimal control over the flow rates of each phase and the flow regime. In a similar manner, for the fabrication of drug releasing particles from biological materials, such as chitosan and human serum, flow focusing junctions are helpful [82,83]. These materials can be fragile, and therefore control over the flow to ensure low shear stress during droplet formation is necessary.

2.2 Droplet formation at T-junctions

T-junctions are one of the most common geometries used for the formation of droplets in microfluidic devices. This geometry is based on two perpendicular channels that connect at 90° to form a T, where one channel carries the outer continuous phase (matrix for emulsion) and the other carries the inner phase (droplet composition). This geometry uses the shear force applied to the inner phase by the outer phase, their relative viscosities, their immiscibility and the relative flow rates to form droplets. It has been reported that T-junction geometries cause more mixing than other geometries for droplet formation, which can affect encapsulation efficiency and particle shape [84,85]. Consequently, this geometry is rarely used for the formation of drug releasing particles. It is also worth noting that this geometry works best on devices not made from PDMS (one of the most commonly used materials for microfluidic device fabrication) since the production of spherical particles can be hindered by the stress applied to the droplet in this geometry and the flexibility of the device material [85,86].

A salient recent example of drug releasing particle formation by means of a T-junction makes use of glass devices for the formation of pH-sensitive hypromellose acetate succinate polymer

microspheres with magnetic characteristics from o/w emulsions, loaded with 5-fluoracil and curcumin [43]. This method enabled the production of multifunctional, complex particles under 50 μm in size. Another example where a T-junction is used for the formation of drug releasing particles is shown in a microfluidic device made from laser rubber, which is a novel use of this types of synthetic material for device fabrication [87]. Laser rubber devices can effectively form droplets, but present similar challenges to PDMS in terms of the size and shape consistency.

2.3 Droplet formation using coaxial geometries

Coaxial geometries for droplet formation are similar to flow focusing geometries but are 3-dimensional. Instead of following a planar design like previous examples, coaxial geometries use capillaries, mostly made of glass, which can be placed inside one another to generate droplets. The flow regime can be altered by modifying the diameter and length of the capillaries. Droplet formation is accomplished by using different flow rates between each of the phases, increasing the shear stress applied to the disperse (droplet) phase and forming droplets in a similar manner to the droplet break-up mechanism found in flow focusing geometries [88,89]. However, when using coaxial geometries, droplets are directly formed in the dispersed phase, with no interaction between the droplets and the surface of the microfluidic device [88]. Coaxial geometries are useful for the formation of multiple emulsions for the fabrication of complex drug releasing particles, since the surface interaction with the microfluidic device material is minimized [89].

This droplet formation geometry has been commonly used for the fabrication of nano-sized drug releasing particles, as the droplet formation is not subject to capillary forces from the surface of the microfluidic device. For example, Xu *et al.* fabricated nanoparticles from PLGA using a coaxial capillary microfluidic device [90]. This device showed the efficient production of drug-loaded PLGA nanoparticles, where the particle size could be tuned and the production throughput was high enough for industrial applications [90,91]. Zhu *et al.* showed that rapamycin loaded PLGA microparticles could also be produced using a coaxial microcapillary device [92]. This device had an encapsulation efficiency of 98%, and allowed tuning of the dosage. Di *et al.* fabricated celecoxib nanoparticles using a coaxial microfluidic device, improving solubility and absorption of drugs in aqueous media [93]. This methodology used a short mixing time achieved by using a turbulent jet regime allowed by the coaxial geometry to accomplish the emulsification of celecoxib [93].

2.4 Other microfluidic device features

Additional features can be added to microfluidic platforms for the formation of drug releasing particles. For example, efficient mixing is a challenge in microfluidic devices because flow is laminar and hence mixing occurs primarily by diffusion. Accordingly, specialized device designs must be used for rapid mixing and these can be passive or active. The simplest type of passive mixing, where no external forces are applied, can be accomplished by co-flowing two or more phases in a channel, but since the mixing is limited to diffusion, very long channels are needed for complete mixing of the phases. A more space efficient solution for passive mixing uses physical geometries to increase the contact area between the phases. A common geometry for passive mixing is the staggered herringbone mixer (SHM) where rectangular grooves are created in the channels, allowing chaotic mixing but maintaining the same pathlength for the fluids (Figure 2) [94]. This SHM geometry has been widely adopted due to the efficient mixing it provides. Work by Meikle *et al*. shows a modular microfluidic cartridge with a SHM design used to fabricate PLGA unloaded and rifampicin loaded nanoparticles [95]. The SHM allowed for fast mixing of the phases to achieve emulsification and to induce precipitation of the polymer. On the other hand, active mixing can be achieved by the application of external forces, such as mechanical mixing, pressure or the inclusion of magnetic or electric fields, all of which can be directly integrated into the microfluidic device [96]. Bokharaei *et al.* showed the high-throughput encapsulation of bovine serum albumin (BSA) into PLA microspheres with an efficiency of up to 96% [97]. In addition, by integrating parallelized mixers in the microfluidic device, this platform has the potential for production scale-up to an industrial scale.

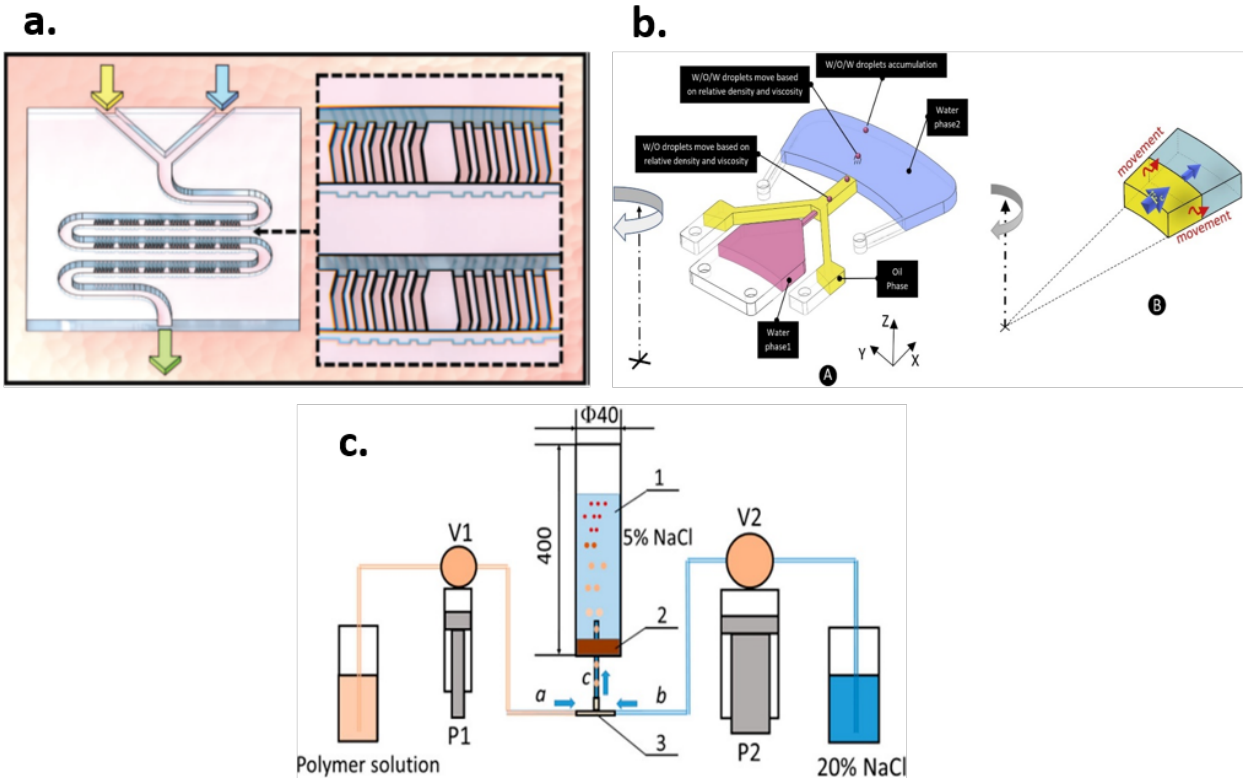

Figure 2. Examples of microfluidic device features used for the fabrication of drug releasing particles. a) Microfluidic device with Staggered Herringbone Mixers (SHM) for the fabrication of drug loaded PLGA nanoparticles. The yellow and blue arrow show the injection of aqueous and polymer solutions respectively, followed by a set of SHM, and the green arrow shows the outlet of the device where the nanoparticles exit. The inset shows the details of the SHM in the channels. Republished with permission of CSIRO Publishing, from [95]; permission conveyed through Copyright Clearance Center, Inc. **b)** Schematic of a microfluidic device designed to be mounted onto a rotating platform for pumping used for the formation of alginate drug releasing microparticles. W/o/w droplets are formed at a flow focusing junction, with the dispersed phase (water) shown in pink, the first encapsulation phase shown in yellow (oil), and the second encapsulating phase shown in blue (water), the inset shows the direction of the centrifugal forces acting on the phases. Reprinted from [98], with permission from Elsevier. **c)** Schematic of a microfluidic device made using a glass dissolution column for the formation of multiple polymer drug releasing microparticles, where P1-V1 and P2-V2 represent the pumping-valving system couple for each phase; a, b and c show the flow direction of the polymer, aqueous and emulsion, respectively; and 1 and 2 are the dissolution column and the stopper controlling flow direction. Reprinted with permission from [99]. Copyright 2017 American Chemical Society.

A different method for the formation of droplets is shown in recent work by Chen *et al,* where curcumin loaded microspheres comprised of poly(caprolactone)-block-poly(ethylene oxide) had a 30% improvement in the encapsulation and drug loading of curcumin, compared to the same particles made in batch [40]. This microfluidic device used segmented flow with Argon gas as the continuous phase (instead of the usual oil continuous phase) to form plugs of the dispersed phase.

Pumping of fluids in a microfluidic platform can also be done using methods other than pumps. Madadelahi *et al.* used a flow focusing device mounted onto a spinning platform that allowed control over the reaction rate, and the size of the drug releasing particles produced (Figure 2) [98]. The use of centrifugal force allowed the use of solutions with similar densities for droplet formation, which is otherwise challenging to accomplish. Similarly, Zhang *et al.* developed a novel technique to use buoyancy to fabricate highly uniform drug releasing particles [99]. The microfluidic device used a T-junction to mix the two phases, which then flowed into a water dissolution column. By dissolving sodium chloride into the water in the column, the density of the aqueous phase was altered, and hence the polymer dissolved in the organic solvent rose up the column. As the droplets move up the column, they are agitated, and the polymer is extracted and precipitates as polymer particles (Figure 2).

2.5 Increasing the amount of drug releasing particles formed on a microfluidic device

Parallelized geometries use many individual microfluidic droplet generators that work together simultaneously to increase the particle production rate [100,101]. Parallelization plays an important role in making microfluidic technologies suitable for industrial use due to the overall low production rate of droplet generation in microfluidic devices [102]. Therefore, the use of droplet generators in parallel has been established as a standard technique for the scale-up of drug releasing particle production. However, connecting multiple droplet generators in one device can change the fluid dynamics, potentially causing disruptions in the desired product [103]. Hence, microfluidic devices must be specifically designed for parallelization to enable large amounts of uniform drug releasing particles to be produced. Some of these disruptions include hydraulic resistance variations, pressure variations during droplet formation, pumping irregularities, air bubbles and non-uniform particle loading [104]. Particularly, maintaining consistent flow rates

between multiple droplet generators is important for the production of uniformly sized particles [90,105].

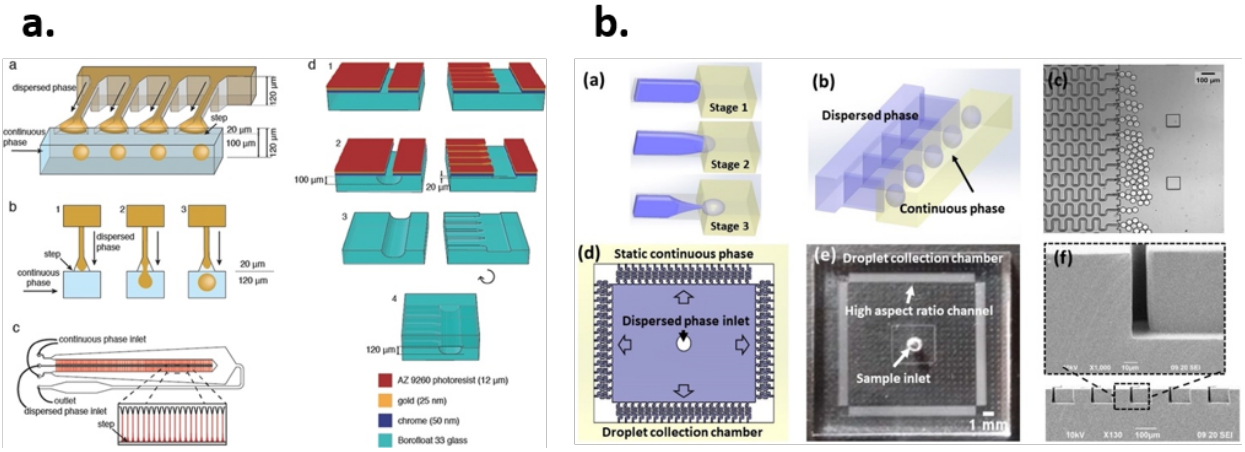

Figure 3. Microfluidic devices used for the large-scale production of drug releasing particles. **a)** Parallelization of 364 T-junctions for the formation of drug releasing microparticles using glass microfluidic devices, where (a) and (b) show a schematic of droplet formation at the junctions (side view and top view respectively), (c) is a visual representation of the complete microfluidic device with each red line representing a single T-junction, and (d) shows the stepwise fabrication process for the microfluidic device. Reproduced with permission from [106], with permission from John Wiley and Sons. **b)** Parallelization of 1,200 flow focusing junctions in a multilayer microfluidic device; where (a) and (b) show different views of the droplet formation mechanism; (c) shows an image of droplet being formed in high throughput; (d) shows a schematic of the device where the dispersed phase (blue) is injected into the center of the device in all four directions and the static continuous phase (yellow) surrounds the microfluidic device; (e) shows the corresponding photo of the microfluidic device, and (f) is a scanning electron microscopy (SEM) image of the cross section of the channels. Reproduced with permission through a Creative Commons Attribution 4.0 International Public License from [46].

Schwendimann *et al.* show a parallelized geometry of 364 T-junction droplet generators used to make monodisperse emulsions for scaled-up production (0.025 L/h) of several different types of particles with different functionalities, such as biodegradable polymeric particles, hydrogel microspheres, and magnetically responsive emulsions (Figure 3) [106]. In another study, Chung *et al.* present a multi-layered microfluidic device for high-throughput droplet generation [46]. This device uses 1,200 parallelized flow focusing junctions to make monodisperse droplets, and droplet formation occurs by sinking the entire microfluidic device into a container full of the outer phase

(Figure 3). Using this device, PLGA microparticles were made using an o/w emulsion at a rate of 25,000 microspheres per second for over 4 hours, thus this process enables efficient production of polymeric drug releasing microparticles.

3. Fabrication of microfluidic devices

The material from which a microfluidic platform is made greatly affects its surface chemistry, the possibility of its commercialization, and the reusability of the device, as well as other aspects such as cost, reproducibility and which features can be included in the device itself, as described in the previous section. Hence choosing the right material is an important component of the overall device design. Microfluidic devices were initially made from materials such as glass, silicon and ceramics. Polymers are currently the most commonly used type of material for device fabrication and include elastomers and thermoplastics as the main categories, with the elastomer PDMS being the most universally used material in academic laboratory settings [107]. Thermoplastics used for microfluidic device fabrication include PMMA, polycarbonate (PC), polystyrene (PS), polyethylene terephthalate (PET) and polyvinyl chloride (PVC). In addition, materials such as metals, cyclin olefin copolymer (COC), the photoresist SU-8, polyimide, and hydrogels can be used for device fabrication. Multiple reviews have summarized the various materials used in the manufacture of microfluidic devices [108–110].

3.1 Methods of microfluidic device fabrication

The material chosen for the microfluidic device has a great effect on the difficulty of device fabrication. Glass and silicon devices are typically more difficult to manufacture since they are usually wet etched individually from hazardous chemicals, whereas devices made from polymers are simpler because they are cast from molds in batch. While glass and silicon are more difficult to work with, they offer advantages not available with other materials, like good optical transparency and solvent compatibility. Microfluidic devices are made using micromachining techniques from computer aided design (CAD) files that indicate the channel design, which is then transferred onto the substrate of choice [3]. Micromachining techniques include photolithography, electron beam lithography, and wet and dry etching (among other methods), most of which require a cleanroom facility [111].

The most common polymer for microfluidic device fabrication is PDMS which is patterned using soft lithography using a mold. The general process of soft lithography includes pattern design in CAD, mask printing onto an acetate film for photolithography, mold fabrication in a cleanroom using the mask, and PDMS device fabrication by pouring the liquid polymer on the mold and then curing it using heat [112]. This process allows for molds to be easily made in academic laboratories and then bonded to polymeric or glass substrates during the channel sealing process. An advantage of soft lithography is that a cleanroom facility is only required for mold fabrication, and other expensive equipment is not required [76]. However, PDMS also has drawbacks in terms of its compatibility with a number of biomaterials. This is caused, firstly, by the limited solvent compatibility of PDMS, which restricts the solvent systems that can be used for the dissolution of particle materials in a microfluidic platform [113]. In addition, proteins and small molecules are susceptible to absorption in PDMS, disrupting the formation and imaging of particles on microfluidic platforms [114].

Hot embossing is a technique used with thermoplastics such as COC or polytetrafluoroethylene (PTFE), where a pattern is made from a master stamp using heat or pressure [111]. Manufacturing the stamp used in this process is time-consuming, but from then on the overall process is easy, fast and inexpensive. The master stamps are typically made from silicon or metal. Plastic microfluidic devices can also be made using injection molding, where a thermoplastic material is melted down and injected into a mold. It is then cooled and removed from the mold, resulting in a device of the same shape as the mold. This process requires complex and expensive machinery, and masters can be time consuming and difficult to make. However, they can be reused for the manufacturing of thousands of devices. Injection molding is the fastest and most inexpensive device manufacturing method currently used for the mass production of microfluidic devices [115]. Laser ablation uses a pulsing laser to remove sections of a thermoplastic material. The desired design can be programmed onto a sheet which the thermoplastic material rests on during manufacturing [111]. This method offers a relatively simple method for making device prototypes.

3D printing has recently been used to make microfluidic devices. This method is simple and fast, with the potential to be used to make a large amount of these devices for industry use [116]. Glick *et al.* used 3D printed molds to produce multi-layered, PDMS microfluidic devices faster and in a

simpler manner compared to other manufacturing techniques [117]. However, it is hard to 3D print device features below around 15 μm [118].

The cost of microfluidic device manufacture depends not only by the material itself but also on the manufacturing method [119]. Glass and silicon are among the most expensive materials as the materials themselves have high costs, and the facilities needed to manufacture them are costly as well [108]. Methods such as injection molding and hot embossing have high start-up costs due to the cost of the instrument and of the molds, but once the process is functional, the cost per device is very low [119].

3.2 Advantages and disadvantages of different materials for microfluidic device fabrication

Glass provides great advantages in terms of optical transparency, chemical and thermal stability, and solvent compatibility [46]. Glass devices allow the fabrication of particles made from a large variety of biomaterials ranging from copolymers such as PCL, PLGA and PLC, to nanofibers and hydrogels such as alginate, chitosan and collagen. This is possible because glass, compared to PDMS, allows for a wider variety of solvents to be used during production of the particles [106]. On the other hand, when working with glass devices it is hard to integrate other on-chip components such valves, and bonding the devices is challenging since high pressure, high temperature and a clean environment are all required [108].

Polymers offer advantages compared to the use of glass such as gas permeability and easy integration of valves and pumps. Types of polymeric materials used for microfluidic device fabrication are listed in Table 1, and include PDMS, PMMA and COC. The main elastomer (and polymer) used in device fabrication is PDMS, which is easy to obtain and relatively inexpensive. This material has good gas permeability, elasticity, sealing properties, can be easily bonded to itself or to glass, and can allow for the integration of on-chip microvalves and micropumps [112]. Disadvantages of this material include low solvent and acid/base resistivity, evaporation of sample, absorption of samples into the device material, and hydrophobic recovery [107]. PDMS devices can also suffer from channel deformation due to its high mechanical compliance, and the solvents that can be used with PDMS are much more limited when compared to glass as many solvents will swell and damage PDMS devices [113].

Thermoplastics used for microfluidic device fabrication include PMMA, PC, PS, PET, PVC, COC, and PTFE, which in general offer mechanical stability, low water-absorption, organic solvent and acid/base resistivity [92]. One general disadvantage of thermoplastics is that they are not good for making valves or multi-layered devices [106]. Thermoplastics such as COC and PTFE give advantages in that they are chemically resistant to even strong solvents, so channels made from these materials will not swell during droplet formation [36]. On the other hand, the thermoplastic PMMA is not chemically resistant so strong solvents will cause deformation of channels made of this material, resulting in changes in fluid flow and droplet generation [36]. Table 1 summarizes the general advantages and disadvantages of each category of device material.

Type of Material	**Examples**	**Advantages**	**Disadvantages**
Inorganic	Glass, silicon, ceramic	- stable - optical transparency (glass) - solvent compatibility - chemical and thermal stability	- costly - not easy to integrate valves - not easy to make multi-layered devices
Elastomers	PDMS	- inexpensive - gas permeability - elasticity - valves and micropumps can be easily integrated - multi-layered devices can be made	- low solvent and acid/base resistivity - evaporation or sample absorption - hydrophobic recovery - channel deformation - limited solvent compatibility
Thermoplastics	PMMA, PC, PS, PET, PVC, COC, PTFE	- inexpensive - mechanical stability - low water absorption - organic solvent and acid/ base resistivity - chemical stability (COC and PTFE)	- not easy to integrate valves - not easy to make multi-layered devices - channel deformation (PMMA)

Table 1. Summary of the advantages and disadvantages of the most common types of materials used for the fabrication of microfluidic devices for the production of drug releasing particles. For each type of material, examples of specific materials used for the fabrication of microfluidic devices, and the associated advantages and disadvantages of each are listed.

4. Avenues for future work

Microfluidic technologies for the fabrication of complex drug releasing particles are clearly advantageous and enabling. However, these methods are in their infancy, and to reach their full potential a number of areas need further research.

More complex particles. As discussed herein, it is possible to use microfluidic devices for the manufacture of drug releasing particles with magnetic properties, responsiveness to pH changes, self-assembly and additional surface properties. However, most methods rely on the use of single-layer droplets. More robust and reproducible methods for the generation of multiple emulsions will further enhance the complexity of particles that can be produced, to allow more targeted transport and delivery of drugs, enhance molecule encapsulation capabilities, and hence create more targeted treatments. The possibility to use a wider variety of biomaterials for particle formation on microfluidic platforms would also be beneficial to the future of the field, which requires the production of these platforms from materials that are more compatible with particle materials such as proteins. This requires the use of polymers that are not PDMS in academic laboratories, or the integration of anti-biofouling coatings into the microfluidic device.

Production scale-up. The production of drug releasing particles in high throughput is necessary to meet the demands of the pharmaceutical industry. Translating academic lab-scale experiments to high-throughput methods will be an impactful addition to this research field. However, this is complicated by the fact that drug releasing particle manufacturing methods developed on materials such as PDMS are not easily translatable to materials such as thermoplastics. A shift in the field to a state where academic research is predominantly performed using commercially viable materials for device fabrication will be an enabling step towards the development of strategies for parallelization towards large-scale production.

Commercialization of microfluidic devices. The main concerns when choosing the microfluidic device material from the perspective of commercialization are cost, whether the material lends itself to mass production and whether the material is robust enough to withstand continuous use for industrial scale production [45]. In addition, microfluidic devices are usually connected to a "lab around the chip", which includes components such pumping systems, microscopes, cameras, sensors, or even other microfluidic devices [120], all of which need to be transferred to a

commercial setting either through miniaturization or through integration with existing instruments at the point of use. An intermediate step would be the creation of a “black-box” microfluidic platform for the manufacture of drug releasing particles that simplifies the lab-around-the-chip and hence allows the use of these technologies outside of specialist laboratories.

5. Conclusions

Microfluidic technologies are an effective and enabling tool for the fabrication of drug releasing particles. It is clear that there are many different designs and avenues for the formation of drug releasing particles in academic laboratories, but that these do not always transfer to industry settings. This could be because academic laboratories tend to develop microfluidic devices using materials and techniques that require substantial modification for use in industry, and do not have the time or funding to develop these further in house. For the same reason, industry might shy away from investing in early-stage technologies that have not been proven to work outside of academic laboratories.

Even so, the pharmaceutical industry has been investing in the integration of microfluidic technologies for the production of drug releasing particles into their production line [121]. A salient recent example is the use of microfluidic technologies to manufacture mRNA lipid nanoparticles for use in vaccines [122]. Over the last year, Pfizer & BioNtech, Moderna, Sanofi and Cure Vac have been developing and releasing vaccines to combat COVID-19 based on mRNA technology. Recently the Canadian government has announced a significant investment in the local biotechnology company Precision Nanosystems for vaccine production based on their nanoparticle technology. Advances such as these highlight the impact that microfluidic technologies can have on the discovery and development of new drug releasing particles in the future. To ensure that this future materializes, avenues for work include narrowing the gap between academic innovation and industry production of microfluidic technologies, specifically with regards to the large-scale production of drug releasing particles and the design of the platforms for the manufacture of smaller and more complex particles from a wider range of biomaterials.

6. Conflicts of interest

There are no conflicts to declare.

7. Acknowledgements

Dr Willerth receives funding from the NSERC Discovery Grant program, the Canada Research Chairs program, the Michael Smith Foundation for Health Research and the Pacific Parkinson's Research Institute. Dr Elvira receives funding from the Canada Research Chairs program, and the Michael Smith Foundation for Health Research Scholar program in partnership with the Pacific Alzheimer Research Foundation. Alejandro Forigua is funded through Dr Elvira's NSERC Discovery Grant.

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