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3D-printed microfluidic droplet generation systems for drug delivery applications

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ABSTRACT

Drug delivery systems are advanced methods that aim to deliver a targeted drug to a specific location or release it at a controlled rate. Many methods have been proposed for drug delivery systems, among which microfluidic systems present unique advantages. In contrast to bulk methods, in this work, by considering the unique capacity of microfluidic-based drug delivery systems, including controllability of fabricated chip geometry and flow rate of multiphase fluid, highly stable particles with higher encapsulation efficiency can be generated. Employing additive manufacturing in biomedical applications has enabled researchers to propose novel and accurate microfluidic systems. In this paper, by employing stereolithography (SLA) and fused deposition modeling (FDM) 3D printing, a microfluidic-based drug delivery system for generating polycaprolactone (PCL) droplets loaded with dexamethasone drug is fabricated. Scanning electron microscope (SEM) images and microscopic images show the effectiveness of this method in generating such droplets.

1. Introduction

Drug delivery systems include a broad range of technologies and methods with the involvement of engineering and medical science to facilitate and increase the speed of pharmaceutical compounds, achieve efficient treatment, and reduce the period of pharmaceutical prescribing [1–3]. Over the past decades, the advantages and applications of drug delivery devices on the micro and nanoscale in the medical and pharmaceutical industries have been identified and increased at a noticeable speed [1,4].

Some of the emerging applications of drug delivery devices include disease diagnosis, disease therapy facilitation, high control in pharmaceutical components or gene analyses, efficient treatment, and reduced therapy time for various diseases [5,6]. Recently, modern drug delivery systems can control the processes of injection, absorption, distribution, and elimination of drugs or genes. In this regard, researchers are always trying to propose new approaches and devices to control the pharmaceutical process [7,8]. Microfluidic devices are one of the most attractive technologies for scientists in all research fields [9]. In recent years, scientists introduced many microfluidic devices into drug delivery systems [10]. Also, microfluidic devices have various applications in biomedical fields, for instance: cancer diagnosis, cell separation, organ on a chip, food industry, tissue engineering, biochemistry [4,11].

Various methods can be employed for the fabrication of microfluidic devices. The most typical methods are soft lithography and additive manufacturing (AM), in which choosing between the fabrication methods depends on the size, accuracy, and application. Additive Manufacturing, also known as three-dimensional (3D) printing, has been considered a new approach that has great potential in biomedical applications [12]. A 3D object, even on a micro scale, can be fabricated with AM by a layer-by-layer method [13–17]. Furthermore, it has the potential to greatly simplify fabrication steps with fine features at a much lower cost and time [18–20]. 3D-printed microfluidic devices can be specially designed for

Abbreviations: PCL, Polycaprolactone; SEM, Scanning electron microscope; FDM, Fused Deposition Modeling; SLA, Stereolithography; PDMS, Polydimethylsiloxane; AM, Additive manufacturing; PLA, Polylactic acid; PVA, Polyvinyl alcohol.

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applications such as: controlling the release of pharmaceutical components, dosing to specify target and less side effect [21,22].

In this article, stereolithography (SLA) and fused deposition modeling (FDM) 3D printing techniques were used to generate polycaprolactone (PCL) droplets loaded with the drug. In this regard, the microfluidic mold was printed with the SLA method, and the support was printed with the FDM method for further microfluidic preparation stages. Since dexamethasone has many biomedical applications, it was chosen as the purpose drug in this paper. Also, a flow focusing microfluidic droplet generation system was used to provide PCL-dexamethasone spheres.

2. Materials and methods

2.1. Materials

PCL and chloroform were purchased from Merck, and polydimethylsiloxane (PDMS) was obtained from Sylgard 184, Dow Corning. The resin was purchased from JamgHe. PLA filament was purchased from YOUSU. Isopropanol and ethanol were purchased from Sigma/Merck. Polyvinyl alcohol (PVA) 96 % powder is purchased from Sigma Aldrich.

2.2. Mold fabrication

Different 3D printing techniques can be implemented to fabricate 3D features. One of the most common methods used is SLA. The SLA printing is desirable and affordable, which was assisted with computer design software (SolidWorks Inc. - Dassault team). In this regard, an SLA printer with a resolution of 50 μm in the vertical and horizontal directions was used. Fig. 1.A illustrates the printed microfluidic mold.

2.3. PDMS casting

To prevent overflowing PDMS during casting, support was designed with the FDM printing method. Fig. 1.B illustrates printed support for casting PDMS. Next, PDMS and a curing agent were combined at a ratio of 10:1. The PDMS mixture was poured into a mold embedded with support to cover the entire mold. Then the support was placed in a vacuum chamber for about 1 h to remove bubbles inside the PDMS. Following that, all the structures were placed on a hot plate at 70 ∘C for 4 h. Then the prepared PDMS chip was peeled off from the mold and punched to have inlets and outlets (Fig. 1.C). The punched PDMS channel bonded to the glass with oxygen plasma (Fig. 1.D).

2.4. Generation of droplets

This chip consists of a 5 % PVA solution as the first phase and a homogenous mixture of PCL, chloroform, and dexamethasone as the second phase. A combination of the PCL and the chloroform, 1:5 wt ratio (10gr chloroform and 2gr PCL), was mixed for about 1 h [23]. Next, the dexamethasone was added to a homogenous

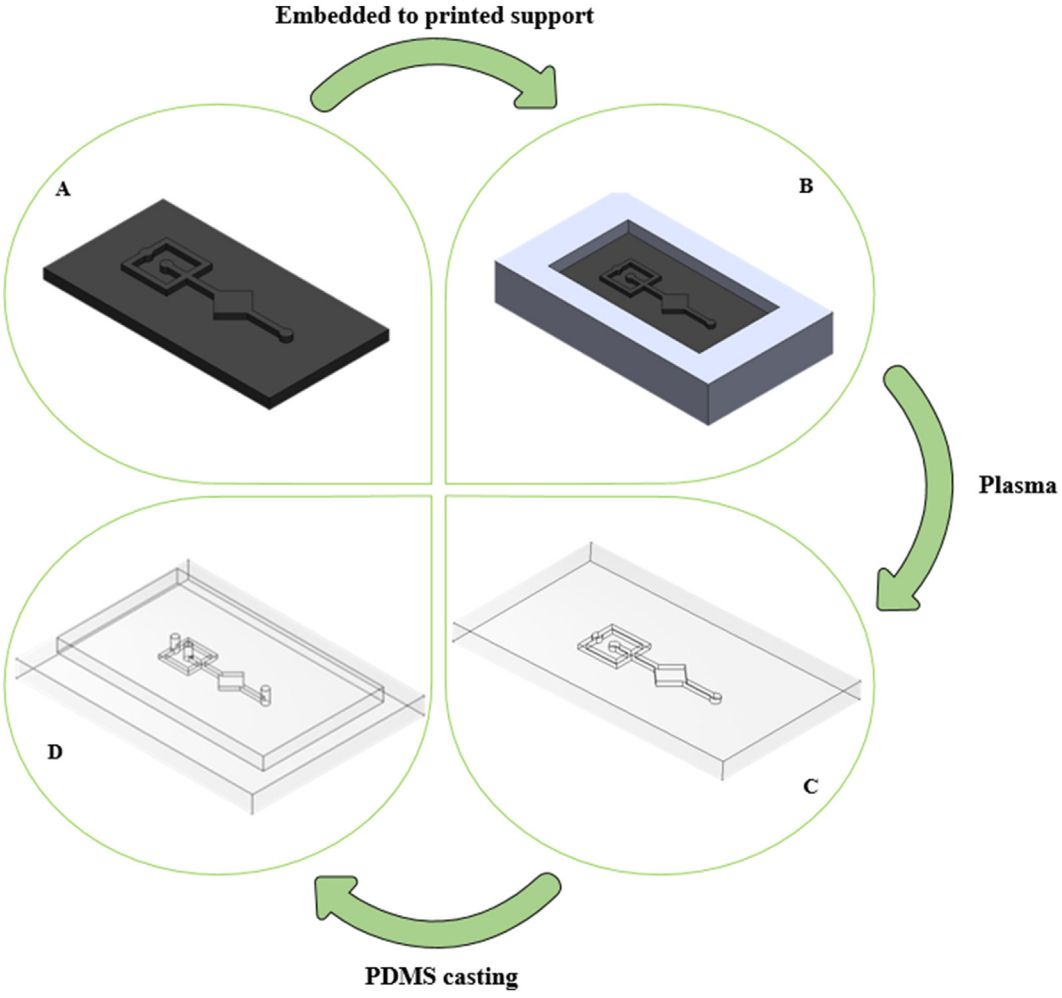

Fig. 1. A schematic of (A) 3D-printed mold, (B) embedded mold to 3D-printed support, (C) casted PDMS, (D) final chip.

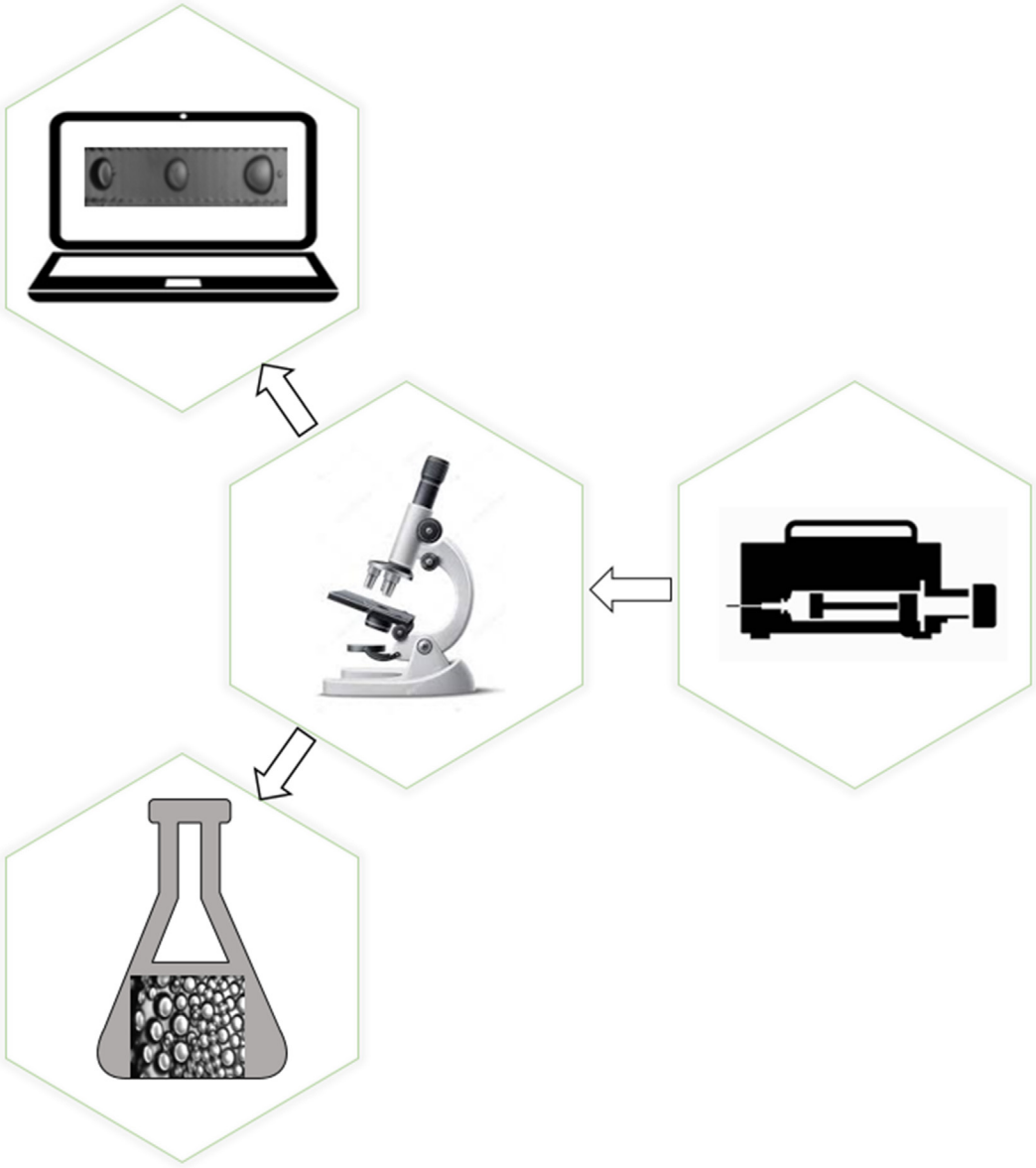

Fig. 2. Experimental setup for testing droplet generation chip.

fluid and mixed for about 30 min. Briefly, the PVA solution and the chloroform solution were injected using two syringe pumps (Sama Company) with 500 μL/min and 200 μL/min flow rates, respectively. A Xiema microscope video camera is used to record the videos. Fig. 2 presents the setup scheme of this system.

3. Results and discussions

As mentioned before, droplets are made of chloroform, PCL, and dexamethasone, and the continuous phase is a 5 % PVA solution. Fig. 3.A illustrates the droplet generation in the aforementioned condition, and as can be seen, droplets are monodispersed. Fig. 3. B shows the collecting chamber at the end of the channel, which was provided for better analysis. Fig. 3.C shows the droplets at the reservoir before evaporation, and high monodispersity can be seen. After chloroform evaporation, FESEM is used to analyze PCL solid spheres. Fig. 3.D and 3.E are SEM images of the PCL-drug spheres with 100-μm and 1-millimeter scale bars, respectively. Image processing from the SEM images shows that the average diameter of the spheres is 150 μm. Results show that this assisted 3D-printed chip can generate PCL-droplets loaded with dexamethasone, which can be used in drug delivery applications. Also, changing microfluidic geometries can generate various ranges of droplet sizes that have different drug-releasing rates and can be used for different target drugs.

4. Conclusion

The microfluidic system was successfully fabricated by employing additive manufacturing technology, particularly use of the FDM and SLA methods. The obtained results from SEM and microscopic images show the succession of fabricated chips in generating PCL droplets loaded with the dexamethasone drug.

CRediT authorship contribution statement

Reza Noroozi: Conceptualization, Visualization, Methodology, Formal analysis, Writing - original draft. **Mohsen Mashhadi Kash-**

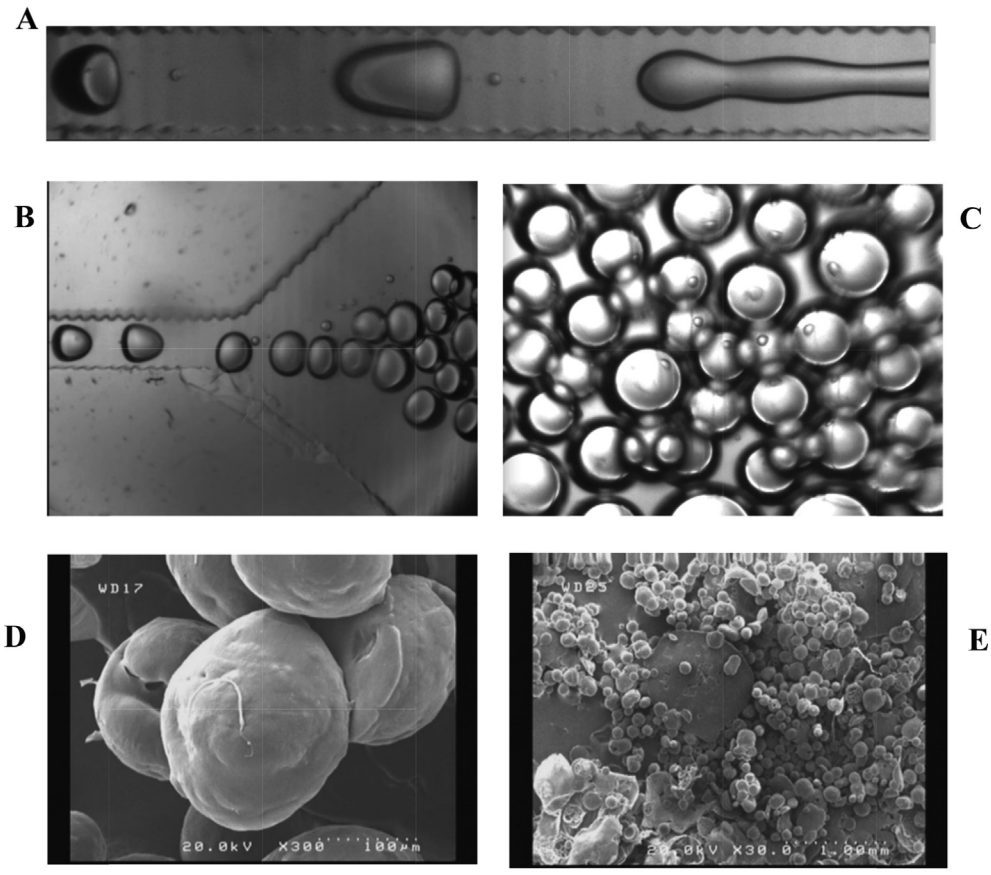

Fig. 3. Images of generated droplets in (A) microchannel, (B) collecting chamber, (C) reservoir, and SEM images of the drug-loaded droplet with (D) 100-µm scale bar, (E) 1-millimeter scale bar.

tiban: Visualization, Methodology, Formal analysis, Conceptualization, Writing - review & editing. **Hadi Taghvaei:** Visualization, Methodology, Formal analysis, Writing – review & editing. **Ali Zolfagharian:** Investigation, Methodology, Writing – review & editing. **Mahdi Bodaghi:** Investigation, Methodology, Supervision, Formal analysis, Writing - review & editing.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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