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Experimental study of manufacturing and characterization of a flow-focusing microchannel to produce thermoresponsive microparticles for on-demand smart drug delivery

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ABSTRACT: In targeted drug delivery, the use of temperature-sensitive micro-drops as drug carriers has recently been considered. In this approach, the use of N-isopropylacrylamide microparticles as temperature-sensitive drug carriers can be effective in the topical treatment of chronic burn wounds and diabetes. In this study, first, a flow-focusing microchannel was fabricated by photolithography. Then N-isopropylacrylamide polymer solution was made with different percentages and used as a drop phase in the microchannel. 10% N-isopropylacrylamide solutions and silicone oil were used as intermediate and continuous phase currents, respectively, and N-isopropylacrylamide microparticles were produced by microchannel. The results of the study showed that by changing the ratio of intermittent to continuous phase flow from 0.14 to 0.84, the diameter of the produced droplets increases from 360 to 515 microns. It was also observed that if the syringe container containing the polymer fluid is kept cold, an aqueous solution containing 10% N-isopropylacrylamide, 0.3% BIS and 4% ammonium persulfate can be used as the drop phase And thus produced temperature-sensitive polymer droplets. Increasing the temperature of the produced micro-drops from 20 to 26° C led to a 50% reduction in their diameter.

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1. Introduction

Microfluidics and its applications in the field of biomedical engineering have been of interest to many researchers. The use of temperature-sensitive biomaterials in targeted drug delivery and topical treatment of infectious and diabetic wounds are some the examples in this field [1, 2].

N-isopropylacrylamide (NIPAM) as one of biomaterials is considered by many researchers in drug delivery field [3-5]. Copolymerization of this material in an aqueous solution can lead to its temperature-controlled behavior. The critical point of this material is about 32°C and can be changed by copolymerizing with other polymers [6-8]. Biocompatibility and Critical temperature compatibility of this material with human skin temperature [9], make this a suitable and usable candidate in the treatment of chronic skin wounds [10]. So in this study, first the poly-NIPAM microparticles were generated using a flow-focusing device. Then the behavior of water adsorption and diffusion was studied.

2. Methodology

This study was performed experimentally. First, a flow-focusing microchannel was fabricated by photolithography. The dimensions of the channel are specified in Fig, 1.

Then NIPAM solutions with different concentrations were made and used in microchannel as drop phase. So the Paraffin oil (containing 20% Span 80) and different NIPAM solutions were used as continuous and drop phase respectively in microchannel to generate NIPAM microparticles. Table 1 shows the NIPAM solutions with different concentrations that were used in the experiment.

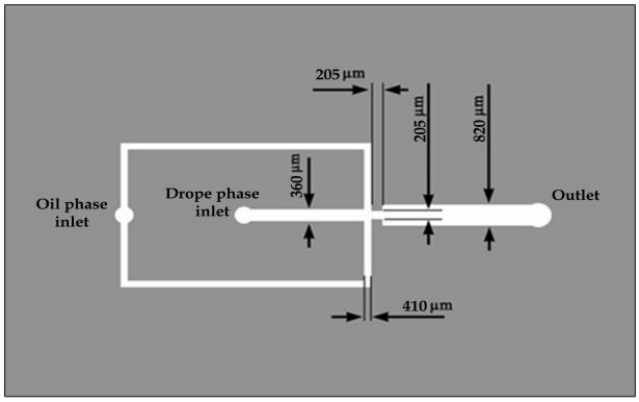

Fig. 1. Flow focusing microchannel dimensions

In order to generate uniform microparticles with the same size, the flow rate ratio between two phases of microchannel was adjusted using syringe pumps. Also in order to prevent polymerization of NIPAM solution in syringe, a cooling chamber was 3D-printed. The syringe cylinder was enclosed inside the chamber. Thus the syringe chamber was kept at a low temperature by circulating water at zero degrees of Celsius by a mini-centrifugal pump. Particles diameter is

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Table 1. NIPAM solutions that be used in experiment

Solution Name	Percent of NIPAM	Percent of BIS[1]	Percent of APS[2]
A	6	0.3	4
B	6	0.3	6
C	8	0.3	4
D	8	0.3	6
E	10	0.3	4
F	10	0.3	6

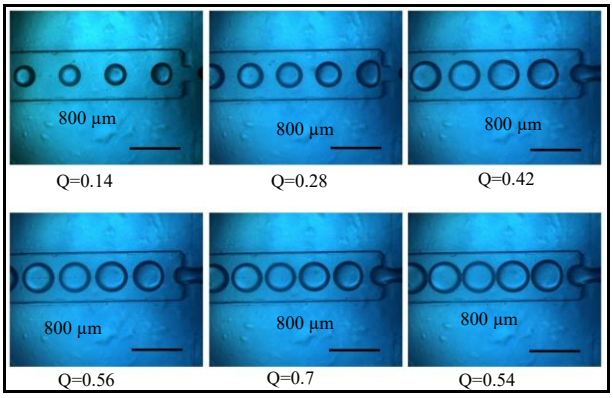

Fig. 2. Images of micro droplets recorded by digital microscope at different flow rates

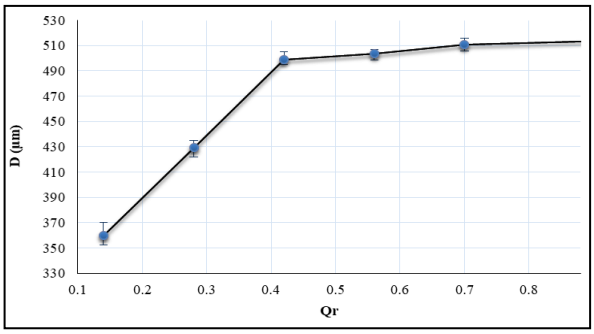

Fig. 3. Diameter of the produced droplets in terms of flow rate ratio at the outlet of channel

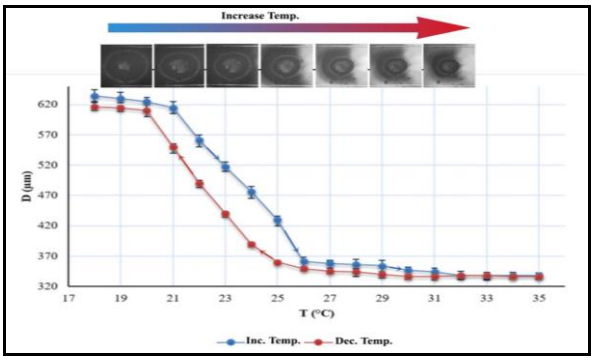

Fig. 4. Microparticles diameter as a function of temp

an important parameter due to its importance of diffusion behavior. So microparticles diameter and center to center distance of them at outlet of channel were measured as a function of flow rate ratio using image processing.

Particles generated collected in a petri dish and kept in 30°C for polymerization. After 4 hours, particles phase changed from aqueous form to jelly form. Then some of particles were randomly selected to investigate their response to temperature. Each particle was placed on a thin glass and a few drops of water were poured on it. Then the glass was placed on a thermoelectric device to control temperature. By change temperature step by step, particles diameters were measured and recorded using image processing.

3. Discussion and Results

The microparticles produced were examined after 24 hours. It was observed that solution "E" has the most suitable physical state among the solutions made. Therefore, solution "E" was found to be suitable for use in microchannel and micro droplets and was named as 10% NIPAM solution. In order to produce micro droplets, the 10% NIPAM solution was reconstituted and stored at 4° C to prevent polymerization. The use of Span 80 as a surfactant in the oil phase showed that it could lead to more stability of the droplets in contact with each other. Fig. 2 shows microscopic images of micro-droplets produced in the microchannel. "Q" is the ratio of polymer phase flow to oil phase flow.

The results showed that with increasing the flow ratio of the two phases, the diameter of the produced droplets increases. The results also show that this increase in diameter is limited to flow rates upper than about 0.42 and its upward trend decreases rapidly.

The results obtained from the diameter of the produced droplets in the outlet of channel are shown in Fig. 3. Examination of the sensitivity of polymerized droplets to temperature showed that increasing the temperature reduces the diameter of the droplets. Diameter as a function of temp is shown in Fig. 4.

4. Conclusions

Diabetic wounds, burn wounds, and deep skin injuries are some of the conditions which can prevent blood and growth factors from reaching the wound bed. Therefore, in such cases, the need to intervene in the treatment process is necessary. Therefore, in this study, the production of temperature-sensitive polymer micro-particles was investigated as a new strategy in the production of smart skin coatings. For this purpose, the combination of NIPAM, BIS and ammonium persulfate in distilled water was used as droplet phase and the combination of liquid paraffin and span 80 was used as a continuous phase. NIPAM microparticles were produced was shown good response to temperature and shown are suitable candidate for drug delivery.

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