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Mass fabrication of size-controllable hydrogel microarrays by dip-pen nanolithography with viscosity-tunable ink

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ABSTRACT

A method of mass fabricating poly(ethylene glycol) (PEG) hydrogel microarrays is demonstrated. Microarrays of poly(ethylene glycol) dimethacrylate (PEG-DMA) with photoinitiator were patterned by one-dimensional (1-D) parallel dip-pen nanolithography (DPN), and the microarrays were cross-linked to form PEG hydrogels by UV irradiation in N_2 air. As an ink material for DPN printing, solid and liquid phase of PEG-DMA were mixed and prepared to tune viscosity of the ink material by temperature. Thus, the diameter of the microarrays was able to be averagely controlled from 1.7 to 6.2 μm as temperature during printing was increased from 25 °C to 37 °C, respectively. The overall microarrays showed less than 16% coefficient of variation (C.V.). Moreover, small molecules, such as fluorescence dyes, were able to be embedded in the PEG hydrogel microarrays.

1. Introduction

Hydrogels have been broadly used as functional materials in various fields [1–5] (e.g., bioengineering, biomedical engineering, and materials engineering) because of their remarkable adaptability to biomaterials. For example, it has been reported that three-dimensional (3-D) hydrogel structures can be used as a scaffold for biomaterials such as bone marrow [6,7], and hydrogel is used as a carrier material for drug delivery into living cells [8–11]. Besides its bio-comparability and highly controllable nature, its strong mechanical properties (e.g., hardness) have also been reported by several research groups [12–15]. In cell studies, mass hydrogel arrays on a surface were used as a template for cell patterning [16,17]. In addition, small molecules embedded in hydrogel arrays can be used as an agent of drug delivery and released into cells, based upon the superior material uptake capability of hydrogels [18–22]. Considering the fact that cell size is generally approximately up to 100 μm in one direction, micro/nanoarrays of hydrogels are at the subcellular scale. Therefore, subcellular scale hydrogel arrays can be applied as cell-binding agents [23]. Moreover, small molecules embedded in hydrogel microarrays are very useful in cell engineering because of their capability to deliver drugs into cells. In particular, subcellular scale hydrogel arrays over a cell size area (>100 μm^2) will be convenient for performing experiments involving the handling of cells. The fabrication of sub-micron poly(ethylene glycol) (PEG) hydrogel arrays using electron-beam processing was reported [24–26]. However, the scale-up of the printing area of sub-micron PEG hydrogel arrays remains challenging.

Herein, we demonstrate that mass microarrays of PEG hydrogels can be fabricated by dip-pen nanolithography (DPN) [27–31] with small embedded molecules; in this study, fluorescence (FL) dye material is embedded into PEG hydrogels to demonstrate the concept. In addition, the size of the PEG hydrogel microarrays is conveniently controlled by manipulating circumstances (mainly temperature) using hydrogel precursor materials with temperature dependent viscosity (new concept of DPN ink materials).

2. Experimental section

2.1. Ink preparation

The hydrogel precursor inks were prepared by mixing the solid (M_W 1000 Da) phase and liquid phase (M_W 500 Da) of poly(-ethylene glycol) dimethacrylate (PEG-DMA) polymers with a weight ratio of 2:1 (solid: liquid). The mixture of PEG-DMA polymers was gently heated (~40 °C) until the solid part clearly melted into the liquid part. About 10 wt% (compared to the total PEG-DMA mixture) of FL dye (Rhodamine B) was mixed into the PEG-DMA mixture; the amount of FL dye can be adjusted from 0.1 to 50 wt%. A small volume (ca. 1%) of the photoinitiator (2,2-

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diethoxyacetophenone) was added to the hydrogel precursor ink just before DPN printing.

2.2. PEG hydrogel DPN printing

Printing of the PEG hydrogel microarrays was carried out with the nanolithography platform (NLP 2000, NanoInk Inc.) with a one-dimensional (1-D) array of 12 pens (M-Exp type, NanoInk Inc.). All printings were conducted on SiO_2 substrate or hexamethyldisilazane (HMDS) spin-coated glass substrate. The PEG hydrogel precursor ink was loaded on the 1-D pen array tip using NanoInk's DPN Inkwell (a device with microchannels for liquid ink dipping). Humidity and temperature during DPN printing were controlled by changing air temperature and humidity (sample stage, inkwell, and pen array tip were put inside of control chamber).

For DPN printing PEG microarrays of 1.7 μm in diameter at 25 °C, excessive hydrogel precursor ink on the pens was removed by bleeding 5–10 times on a blotting substrate before printing. The DPN printing was carried out at 25 °C and 20% relative humidity (R.H.) with a dwell time of 1 s. For printing PEG microarrays of 6.2 μm in diameter, the printing was carried out at 37 °C and 20% R.H. with a dwell time of 0.5 s. This condition resulted in uniform printing of about 25 features with a diameter of around 5 μm. A bleeding step was not executed for these conditions, and the automatic re-inking procedure after 5 × 5 dot arrays was set in the NLP 2000 pattern design tool.

For both sizes of microarrays, the DPN system deposited 3000 hydrogel domains, covering a total area of 0.8 × 0.6 mm^2 on a substrate within 5 min. The DPN printed microarrays on substrate were then exposed to UV irradiation with N_2 gas, purging for 10 min to polymerize the PEG hydrogel precursors and form the PEG hydrogels.

3. Results and discussion

Fig. 1 shows a fabrication process of size-controlled FL dyes embedded in PEG hydrogel dot arrays. First, hydrogel precursors with FL dye molecules are DPN printed on a hydrophobic substrate. Because the hydrophobic surface concentrates the hydrogel precursor ink without spreading it out, it helps to minimize the size of the ink pattern. Hydrogel precursor changes into solid phase from liquid phase with increasing molecular weight at room temperature. Hydrogel precursor ink solution was made by mixing two different molecular weights of PEG-DMA; one is a solid at room temperature and the other is a liquid at room temperature (see Experimental section). The hydrogel precursor ink changes its viscosity depending on temperature [32]; that is, it solidifies as temperature decreases, and it liquidizes as temperature increases. It can be speculated that the lower molecular weight PEG-DMA would probably diffuse from the tip preferentially to the larger molecular weight PEG-DMA. Therefore, the ink diffusion is changed by the temperature during the printing process. Ink diffusion in high temperatures (~37 °C) is faster than that in low temperatures (~25 °C). In other words, the larger dot patterns are printed in high temperatures, and the smaller patterns are obtained by printing in low temperatures. The hydrogel precursor ink is composed mainly of PEG-DMA. The acrylate moiety at the end of the PEG-DMA molecule can be cross-linked by UV irradiation in N_2 air [33,34]. To initiate the cross-linking between the acrylate moieties of the hydrogel precursor ink, photoinitiator molecules are added to the ink solution with a volume ratio of 1:100. Therefore, PEG hydrogel pattern arrays are formed from the cross-linking of DPN printed patterns by UV exposure. In this manner, different sizes of FL dye molecules embedded in PEG hydrogel microarrays can be obtained.

Two different diameters of PEG hydrogel microarrays were able to be printed by 1-D parallel DPN [35,36] (Fig. 2). Fig. 2(a) shows a captured optical microscope picture during 1-D DPN printing of PEG hydrogel precursor ink at 20% R.H. and 25 °C. In this condition, 5 × 200 dot arrays per pen, 1–2 μm in size, can be printed with one inking (see Movie S1). As shown in Fig. 2(e), dot arrays over 5 μm in size can be printed at 20% R.H. and 37 °C. In this condition, 5 × 5 dot arrays per pen were printed from the bottom row to the top row with one inking, and printing continued with the serial automated inking process (see Movie S2). Fig. 2(b) and (c) shows the regular

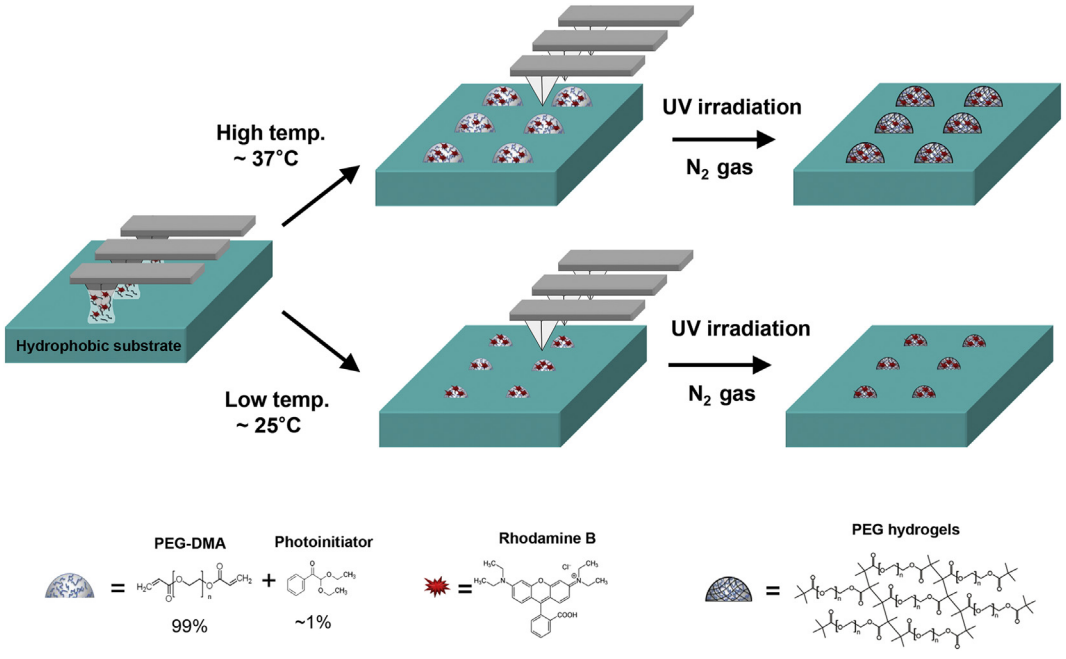

Fig. 1. Schematic representation of PEG hydrogel microarray fabrication. Microarray size is able to be controlled by changing temperature during patterning process. In addition, small molecules like Rhodamine B can be embedded in the PEG hydrogel microarrays.