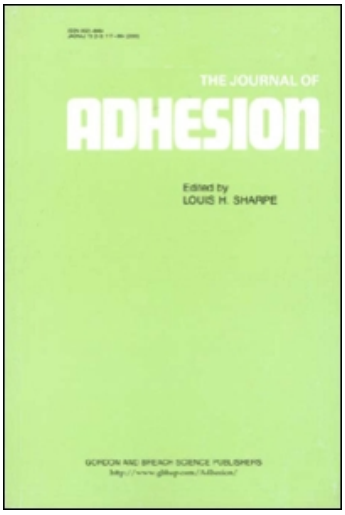

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Microscale Patterning of Two-Component Biomedical Hydrogel

Anand Doraiswamy[a]; Rene Crombez[b]; Weidian Shen[b]; Yuan-Shin Lee[c]; Roger J. Narayan[a]
[a] Joint Department of Biomedical Engineering, University of North Carolina, Chapel Hill, NC, USA [b] Surface Science and Nano-Tribology Laboratory, Eastern Michigan University, Ypsilanti, MI, USA [c] Edward P. Fitts Department of Industrial and Systems Engineering, North Carolina State University, Raleigh, NC, USA

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[1]Joint Department of Biomedical Engineering, University of North Carolina, Chapel Hill, NC, USA
[2]Surface Science and Nano-Tribology Laboratory, Eastern Michigan University, Ypsilanti, MI, USA
[3]Edward P. Fitts Department of Industrial and Systems Engineering, North Carolina State University, Raleigh, NC, USA

In this study, piezoelectric inkjet technology was used for microscale patterning of a two-component medical hydrogel (sold under the registered trademark Coseal®). A MEMS-based piezoelectric actuator was used to control the flow of polyethylene glycol in a sodium phosphate/sodium carbonate solution through inkjet nozzles. A hydrogen chloride solution was subsequently used to cross-link the polyethylene glycol material. Optical microscopy, scanning electron microscopy, atomic force microscopy, Fourier transform infrared spectroscopy, X-ray photoelectron spectroscopy, and nanoindentation studies were performed to examine the structural, chemical, and mechanical properties of the inkjetted hydrogel material. Scanning electron micrographs revealed that the inkjetted material exhibited randomly oriented cross-linked networks. Fourier transform infrared spectroscopy revealed that the piezoelectric inkjet technology technique did not alter chemical bonding in the material. Piezoelectric inkjet printing of medical hydrogels may improve wound repair in next generation eye surgery, fracture fixation, and wound closure devices.

Keywords: Hydrogel; Inkjet; Microfabrication; Piezoelectric

INTRODUCTION

Hydrogels are hydrophilic polymers that are held together by covalent bonds, hydrogen bonds, van der Waals interactions, or

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Address correspondence to Roger J. Narayan, Joint Department of Biomedical Engineering, University of North Carolina, Chapel Hill, NC 27599, USA. E-mail: roger_narayan@msn.com

physical entanglement. These materials often exhibit significant swelling in water or in biological fluids. The integrity of the three-dimensional network in fluid-swelled hydrogel materials is maintained. Polyethylene glycol is created by polymerization of ethylene oxide. This material is soluble in several solvents, including benzene, toluene, and water. Triethylene glycol and larger polyethylene glycol molecules are generally considered to be nontoxic. For example, triethylene glycol and polyethylene glycol oligomers (*e.g.*, PEG-4 and PEG-8) were shown to be not mutagenic in chromosomal aberration assays and mutagenicity assays [1].

Polyethylene glycol and other hydrogels are cross-linked by means of covalent bond formation between chains. Ionizing radiation, photopolymerization, or chemical reactions may be used to generate free radicals and cross-link hydrogels. For example, Silverman *et al.* used ultraviolet light to polymerize a polyethylene oxide adhesive in a rat model [2]. However, radiation-based cross-linking techniques are limited by the fact that the electron beam, gamma ray, or X-ray energy may not penetrate uniformly throughout a given adhesive bond. Chemical processes are more commonly used to generate cross-linking in polyethylene glycol materials. For example, the hydrogel Coseal® (Baxter Healthcare, Fremont, CA, USA) contains two polyethylene glycols, a dilute hydrogen chloride solution, and a sodium phosphate/sodium carbonate solution [3]. At the time of use, the polyethylene glycols, the sodium phosphate/sodium carbonate solution, and the dilute hydrogen chloride solution are mixed to form a cross-linked hydrogel. Strong covalent cross-links may form both within the hydrogel and between the hydrogel and the proteins in surrounding tissues.

Coseal hydrogel sealant has demonstrated impressive leak-free closures in cardiovascular, urinary, and neurological surgery applications [4–6]. Coseal bonds have demonstrated high tissue adhesion strengths and high internal cohesive strengths. Recent studies using a porcine nephrectomy model indicate that Coseal may be able to withstand supraphysiologic pressures [3]. Rapid sealing times (5–16 s) were observed during *in vivo* studies. Glickman *et al.* demonstrated that the sealing for the Gelfoam® thrombin conventional adhesive (Pfizer, Inc., New York, NY, USA) was more than ten times as long as that for the Coseal adhesive [7]. Tissues surrounding the Coseal seals did not exhibit inflammatory behavior. Finally, Coseal bonds resorbed within 30 days after administration [4].

Margalit *et al.* recently examined the use of hydrogels for repairing tears in retinal tissue [8]. In their study, polyethylene glycol exhibited higher adhesive strength than fibrin, Cell-Tak, or photocurable

adhesives. Hydrogels were shown to be nontoxic to retinal tissue in a rabbit eye model. It should be noted that conventionally applied hydrogels have not been approved for use in precise surgical procedures, including ophthalmic procedures. Hydrogel sealants administered using conventional means are currently precluded from use in enclosed spaces, including the intracranial cavity and the eye. Similar concerns have been noted with hydrogel prostheses that are implanted in compression-sensitive regions (*e.g.*, hydrogel intraocular lenses) [8].

In this study, we have examined the use of piezoelectric inkjet technology for microscale direct writing of Coseal polyethylene glycol hydrogel films. The major advantage of inkjet printing over conventional hydrogel patterning techniques is that only sufficient material to form a seal will be introduced to the lesion site. Hydrogel swelling may be minimized, bond lines between tissues may be reduced, and improved bond strengths may be realized. In previous work, we have demonstrated that a micro-electro-mechanical system (MEMS)-based piezoelectric actuator may be used to fabricate a two-dimensional pattern containing mussel adhesive proteins and other biological materials [9,10]. Inkjet printing has also been used to fabricate a variety of three-dimensional structures for biomedical applications, including cell-seeded scaffolds [11]. For example, Campbell and Weiss have described microfabrication of functional three-dimensional tissue substitutes containing cells, hormones, and extracellular materials using inkjet printing [12]. Fourier transform infrared spectroscopy, X-ray photoelectron spectroscopy, and nanoindentation studies were performed to examine the structural, chemical, and mechanical properties of the inkjetted hydrogel material. Piezoelectric inkjet printing technology may greatly improve wound repair in next generation eye repair, fracture fixation, and wound closure devices.

EXPERIMENTAL PROCEDURE

Coseal contains two polyethylene glycol polymers, a dilute hydrogen chloride solution, and a sodium phosphate/sodium carbonate solution, which form a hydrogel upon mixing. The shelf life of Coseal solutions from manufacture is 36 months [13]. The liquid solutions and polyethylene glycol powder components were removed from the syringe assembly and transferred to sterile vials. Polyethylene glycol powder was dissolved in the sodium carbonate/sodium phosphate solution and transferred to an inkjet cartridge (Part I). The other solution (Part II) was transferred into a separate inkjet cartridge. Formation of the low-viscosity hydrogel was accomplished by patterning the Part II solution over the Part I pattern [14].

A DMP-2800 piezoelectric inkjet printer (Fujifilm Dimatix, Santa Clara, CA, USA) was used to dispense picoliter quantities of Part I and Part II solutions in a predefined pattern. The inkjet cartridge contains a lead zirconate titanate unimorph. This unimorph is actuated in the plane of the wafer (bender mode). Drops ejected from the DMP-2800 system are $\sim$10 pL in volume. The cartridge of the inkjet printer (volume = 1.5 mL) is equipped with sixteen nozzles (diameter = 21.5 μm), which are located 254 μm apart. The waveform pulse shape (amplitude, slew rate, and duration), frequency, and voltage were independently optimized for the Part I solution and the Part II solution. The solution was calibrated for constant front-velocity ($\sim$10 m/s) for all nozzles prior to deposition. The solutions were inkjetted at 16 V using an optimized waveform. Patterns were made on Si (111), borosilicate glass, and KCl substrates at 25°C and 40% relative humidity.

Atomic force microscopy (AFM) was performed using a Nanoscope IIIa Scanning Probe Microscope (Veeco Instruments, Santa Barbara, CA, USA), which was operated in the tapping mode. Scanning electron microscopy of the hydrogel patterns was performed using a S3200 system (Hitachi, Tokyo, Japan), which was equipped with a Robinson backscattered electron detector. Fourier transform infrared spectroscopy (FTIR) data were obtained using a 5000 s spectrometer (Mattson, Fremont, CA, USA) with 4 cm^{-1} resolution; this instrument was operated in transmission mode. X-ray photoelectron spectroscopy (XPS) data were acquired using an LAS-3000 spectrometer (Riber, Rueil-Malmaison, France), which contains a Mg Kα source ($\lambda = 1254$ eV) and exhibits a 1 mm spot size. In this study, the take off angle was 75° from the surface, the X-ray incidence angle was 20°, and the X-ray source-analyzer angle was 55°. The base pressure in the chamber was $\sim 10^{-10}$ Torr.

A Nano-Indenter XP instrument (MTS Systems, Oak Ridge, TN, USA) was used to carry out indentation tests using a continuous stiffness measurement (CSM) technique. Young's modulus (E) and the hardness (H) values were obtained for the material. The indentation depth was examined under increasing load. A lock-in amplifier was used to examine the differentiation of loading force over the vertical displacement at the vibrating frequency during the indenting process. It eliminates the need for unloading to obtain the slope of the unloading curve at the turning point. As a result, Young's modulus and hardness are measured continuously instead of at a discrete set of loads and depths. When the tip indents into the surface of the hydrogel, the tip vibrates at a high frequency. A total of five tests were performed at the scattered sites on the surface, with spacing between indents from 100 μm to 6 mm. Indentations were conducted at depths up to 750 nm.

RESULTS AND DISCUSSION

Coseal hydrogel patterns were achieved in two steps. First, the powder/sodium carbonate solution (Part I solution) was inkjetted into a predefined pattern. The second solution (Part II solution) was subsequently inkjetted over the Part I pattern using a matching pattern. Formation of a hydrogel occurred upon reaction between the Part I and Part II solutions. Figure 1 contains optical micrographs of Coseal hydrogel inkjetted in a circular pattern or a dot pattern on borosilicate glass substrates. The dot pattern shows that ~200 μm features may be obtained using this two-component layer-by-layer approach. Scanning

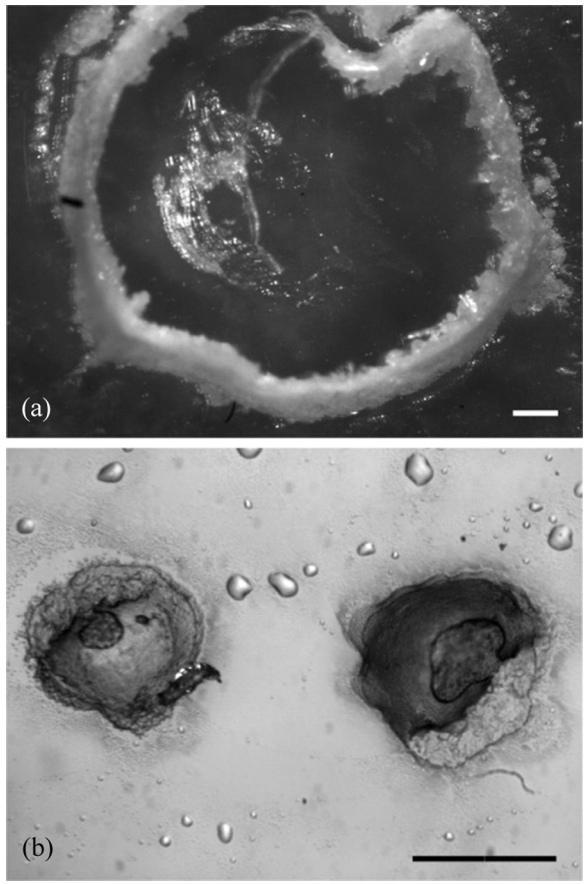


FIGURE 1 Optical micrograph of Coseal material inkjetted in (a) circular pattern or (b) dot pattern on borosilicate glass substrates. Scale bar = 200 μm.

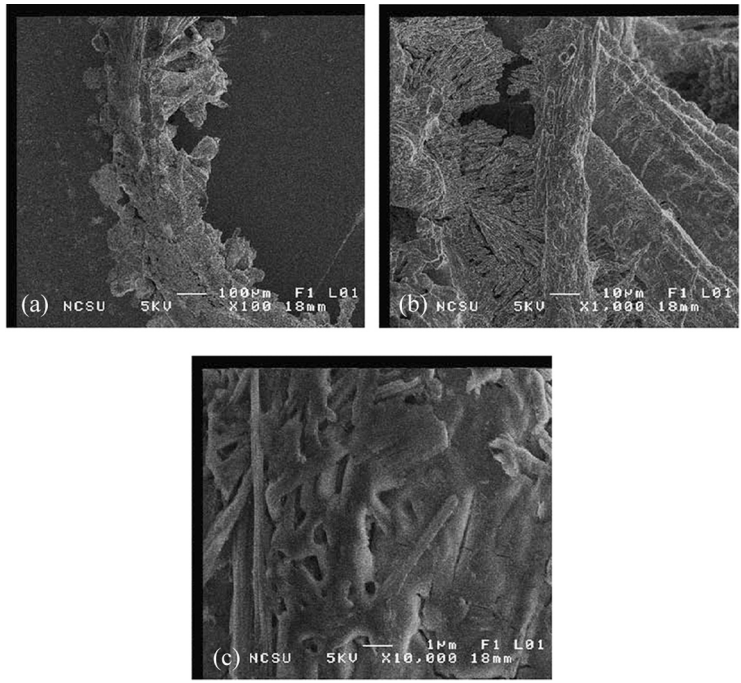


FIGURE 2 Scanning electron micrographs of Coseal material inkjetted in circular pattern on Si (111) substrates at several magnifications.

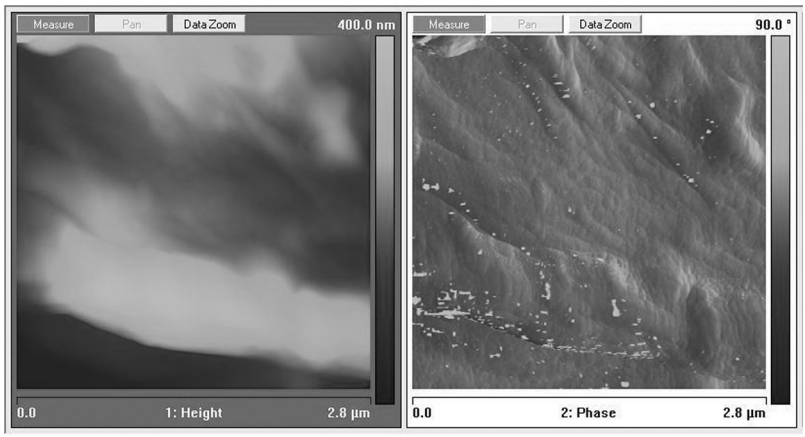


FIGURE 3 (Left) $2.8 \times 2.8\,\mu m$ topographic image of inkjetted Coseal material on silicon (111) substrate. (Right) Phase image of inkjetted Coseal material.

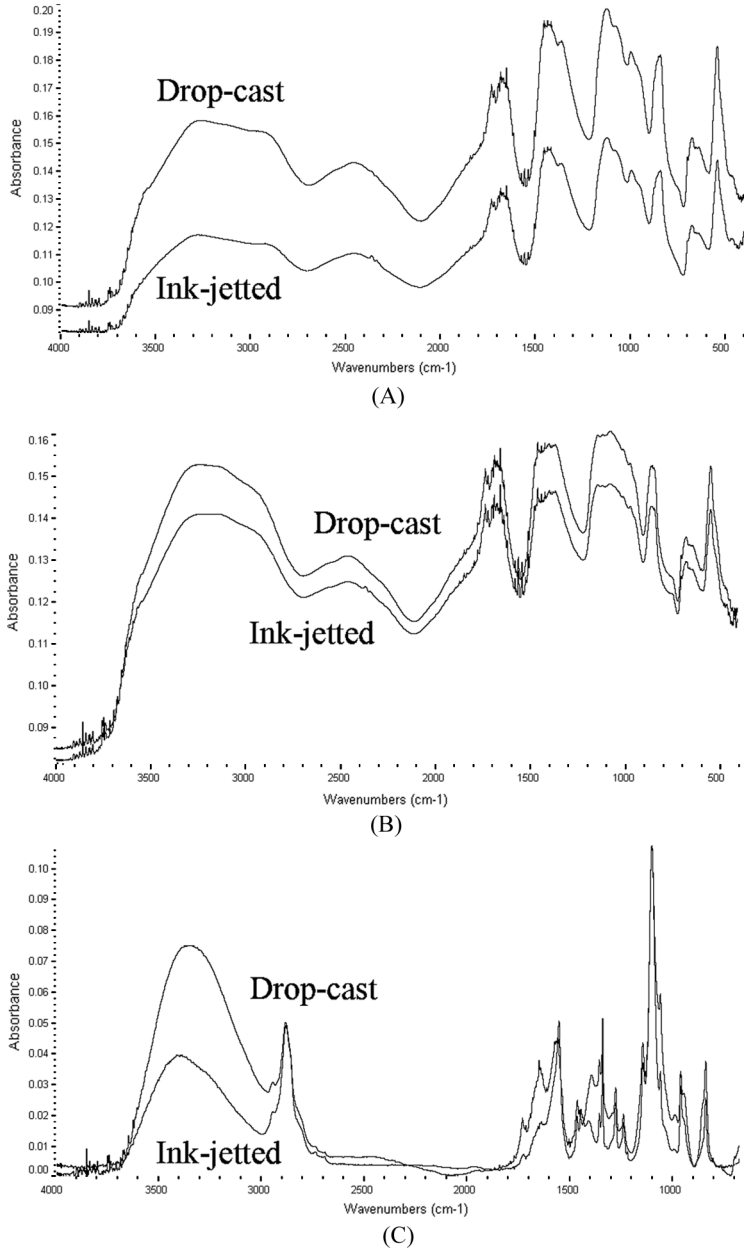


FIGURE 4 Fourier transform infrared absorption spectra overlay of inkjetted and drop-cast Coseal materials. (A) Part I. (B) Part II. (C) Part I + Part II (Coseal hydrogel formed by mixing the two components).

electron micrographs of Coseal material inkjetted in a circular pattern on Si (111) substrates at several magnifications are shown in Fig. 2.

The width of the circular pattern varied from 300 to 400 μm. Uneven shrinkage and swelling of the hydrogel material were noted. In addition, randomly oriented cross-linked networks were observed in the hydrogel patterns. A three-dimensional representation of the topography micrograph (Fig. 3) revealed dome-shaped features in the hydrogel pattern; a peak height of ~5.50 μm was observed. The phase image reveals ~1–6 μm round-shaped interconnected islands, which exhibit nonuniform height values. The average surface roughness (S_a) over the 20-μm scan-range was shown to be 0.258 μm, with root mean square (S_q) of 0.345 μm. Dong *et al.* have indicated that smaller drop sizes may be obtained using inkjetting materials with higher viscosities [15]. In addition, Doggart *et al.* have indicated that the resolution of features produced by inkjet printing may be improved by increasing the viscosity of the inkjetted material [16].

Fourier transform infrared (FTIR) absorption spectra overlay of drop-cast material and the inkjetted material are shown in Fig. 4. There is no significant difference in the O–H stretch mode (~3500 cm^{-1}), C–H stretch mode (2890 cm^{-1}), C=O stretch mode (1745 cm), CH_2 modes (1500–1300 cm^{-1}), and C–O stretch mode (1110 cm^{-1}) between the inkjetted and drop-cast solutions. Figure 5 contains X-ray photoelectron spectra of inkjetted Part I solution and inkjetted Part II solution on silicon (111) substrates. The spectra revealed the presence of C (45.8%), O (35.0%), Si (18.6%), and Na

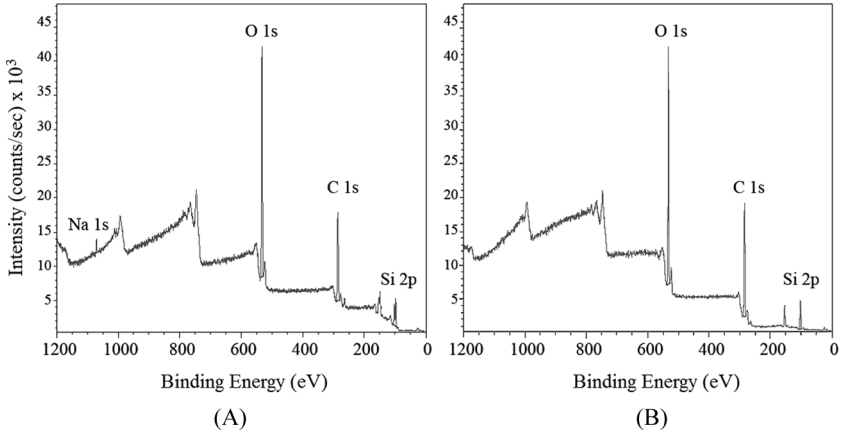
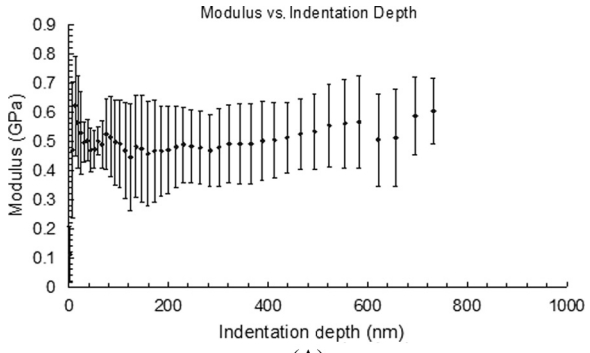
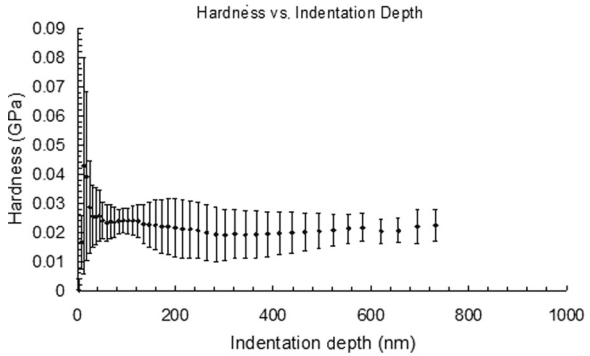


FIGURE 5 X-ray photoelectron spectra of inkjetted Coseal material on silicon (111) substrate. (A) Part I. (B) Part II.



(A)



(B)

FIGURE 6 (A) Modulus vs. indentation depth of inkjetted Coseal material on silicon (111) substrate. (B) Hardness vs. indentation depth of inkjetted Coseal material.

(0.6%) for PEG-powder solution (Part I) and the presence of C (57.4%), O (31.3%), and Si (11.4%) for the other solution (Part II). No evidence of lead release from the lead zirconate titanate unimorph was noted. Figure 6 contains the hardness and Young's modulus values for Coseal material inkjetted on a silicon (111) substrate. These values are similar to those obtained by Chiarelli *et al.* for polyvinyl alcohol-polyacrylic acid hydrogels (Young's modulus ~750 kPa), and are significantly higher than those obtained by Kim *et al.* and Opdahl *et al.* for poly-HEMA-MA hydrogels (~470 kPa) [17–19].

CONCLUSIONS

Piezeolectric inkjetting was shown to be a non-contact and non-destructive technique for controlled administration of two-component

surgical sealants. Unlike conventional microscale processing techniques, piezoelectric inkjetting does not chemically alter the hydrogel, introduce toxic materials, or heat the material. *In situ* cross-linking enables microscale patterning of hydrogel materials. Printing of small spatially aligned drops may potentially enable bond lines between materials to be reduced and the number of medical applications to be increased. Future studies are envisioned that will involve determining the influences of surface chemistry and surface roughness on spreading of Coseal hydrogel patterns. Piezoelectric inkjet printing of medical hydrogels may improve wound repair in next generation eye surgery, fracture fixation, and wound closure devices.

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