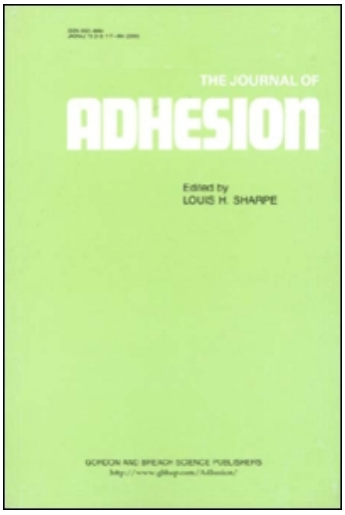

The Journal of Adhesion
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713453635

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Online publication date: 05 February 2010

To cite this Article Doraiswamy, Anand , Crombez, Rene , Shen, Weidian , Lee, Yuan-Shin and Narayan, Roger J.(2010) 'Inkjet Printing of Cyanoacrylate Adhesive', The Journal of Adhesion, 86: 1, 1 — 9
To link to this Article: DOI: 10.1080/00218460903417651
URL: http://dx.doi.org/10.1080/00218460903417651

The Journal of Adhesion, 86:1–9, 2010

ISSN: 0021-8464 print/1545-5823 online
DOI: 10.1080/00218460903417651

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Inkjet Printing of Cyanoacrylate Adhesive

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In this study, we have demonstrated the use of piezoelectric inkjet printing to fabricate microscale patterns of Vetbond® n-butyl cyanoacrylate tissue adhesive. Optical microscopy, atomic force microscopy, nanoindentation, and a cell viability assay were used to examine the structural, mechanical, and biological properties of microscale cyanoacrylate patterns. The ability to rapidly fabricate microscale patterns of medical and veterinary adhesives will enable reduced bond lines between tissues, improved tissue integrity, and reduced toxicity. We envision that piezoelectric inkjet deposition of cyanoacrylates and other medical adhesives may be used to enhance wound repair in microvascular surgery.

Keywords: Medical adhesives; Microfabrication; Piezoelectric inkjet printing

INTRODUCTION

A current challenge in microvascular surgery involves closing of small blood vessels or end-to-end joining of blood vessels. The conventional technique for joining blood vessels involves the use of sutures. Conventional suturing techniques are generally considered to be successful;

Received 19 January 2009; in final form 24 July 2009.
One of a Collection of papers honoring J. Herbert Waite, the recipient in February 2009 of *The Adhesion Society Award for Excellence in Adhesion Science, Sponsored by 3M*.
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these techniques are associated with a 90–95% success rate. On the other hand, suturing techniques involve damage to the blood vessel endothelium, which is associated with several clinical complications, including foreign body reaction, platelet aggregation, distortion of the blood vessel, and ischemia of the blood vessel wall [1]. Endothelial lacerations can lead to the development of strictures at locations where blood vessels are being joined; these strictures may result in failure of grafted tissue [2]. In addition, suturing is a time consuming process; surgical delays associated with the suturing process may lead to tissue damage.

An alternative joining technique that has gained support in recent years involves the use of adhesives, which hold tissue together for several weeks while tissue regrowth processes take place. It is thought that adhesives may be used to perform joining of blood vessels with easier tissue manipulation and fewer complications than conventional suturing techniques. For example, fibrin glue has previously been utilized for joining blood vessels [3,4]. The components obtained from pooled human plasma (fibrinogen, factor XIII, and thrombin) undergo various clinical virus safety, manufacturing, and pasteurization measures. However, there are several safety issues that have limited the use of these materials, including the possibility of disease transmission and anaphylactic reaction. For example, concerns exist regarding the transmission of hepatitis viruses, human immunodeficiency virus, human T-cell lymphotropic virus-1, Parvovirus B19, bovine spongiform encephalopathy, and other pathogens from blood-derived materials.

Several medical applications for N-butyl cyanoacrylate were demonstrated by Leonard and his colleagues at the Walter Reed Army Medical Center, including joining of tissues, joining of blood vessels, and hemostasis of wounds [5–7]. For example, Matsumoto *et al.* demonstrated that N-butyl cyanoacrylate is effective for hemostasis of kidney wounds and liver wounds, which enables shorter operating times and simpler surgeries than the conventional suture method [8–10]. Joining of tissues with N-butyl cyanoacrylate was also associated with less blood loss than the conventional suture method [11]. Recent work by Saba *et al.* suggests that N-butyl cyanoacrylate is a suitable alternative to conventional suturing for joining of blood vessels [12]. N-butyl cyanoacrylate may be suitable for use in microvascular surgery as it is currently used for embolization of arteriovenous malformations as well as for treatment of bleeding associated with gastic varices [13,14]. We have recently demonstrated that piezoelectric inkjet printing is a non-contact and non-destructive technique for patterning many biological materials. In our previous work, piezoelectric jetting was used to develop microscale patterns of several

biological materials, including streptavidin protein, sinapinic acid, deoxyribonucleic acid, marine mussel adhesive protein, multiwalled carbon nanotube/DNA hybrid materials, and monofunctional acrylate esters [15–17]. Fourier transform infrared spectroscopy studies of inkjetted and dropcast marine mussel adhesive protein, n-butyl cyanoacrylate, and 2-octyl cyanoacrylate demonstrated similar peak intensity values, which suggests that piezoelectric inkjet printing does not significantly alter the structure of these materials [16,17]. In this study, piezoelectric ink-jet technology was used to investigate piezoelectric inkjetting of Vetbond® b-butyl cyanoacrylate tissue adhesive. The patterned materials were examined using optical microscopy, atomic force microscopy, nanoindentation, and a cell viability assay. We envision that piezoelectric inkjet deposition of cyanoacrylate adhesives may be used to enhance wound repair in microvascular surgery. For example, piezoelectric inkjet printing may enable processing of adhesive patterns in closed chest coronary artery bypass graft surgery and in other surgeries that involve limited surgical access [14].

MATERIALS AND METHODS

Vetbond® tissue adhesive (3M, St. Paul, MN, USA) contains n-butyl cyanoacrylate (>98%), hydroquinone (<1%), and blue dye (<0.01%). A DMP-2800 piezoelectric inkjet printer (Fujifilm Dimatix, Santa Clara, CA, USA) was used to dispense picoliter quantities of Vetbond tissue adhesive onto a silicon (111) substrate. The cartridge contains a patterned lead zirconate titanate unimorph; this device is actuated in the plane of the wafer (bender mode). Drops ejected from this system are ~10 pL in volume. The inkjet printer cartridge has a volume of 1.5 mL. The cartridge is equipped with 16 individually addressable nozzles (nozzle diameter = 21.5 μm), which are spaced 254 μm apart. The waveform pulse shape (amplitude, slew rate, and duration), frequency, and voltage were optimized for the solution. The droplet flight (distance traveled) from the nozzle was examined using an ultra-fast camera, which is located in a plane that is situated perpendicular to the substrate (Fig. 1). Data from the camera may be employed to modify the voltage waveform, which governs the velocity and the shape of the drops that are ejected from the nozzles. The adhesive solution was purged out and calibrated for constant front-velocity (~10 m/s) for all nozzles prior to deposition. The Vetbond tissue adhesive was inkjetted at 16 V using an optimized wave-form into dot array patterns and other microscale patterns at 25°C and 40% relative humidity. Optical imaging of the deposited adhesives was performed using an upright microscope (Olympus Inc., Center Valley, PA, USA). Atomic force

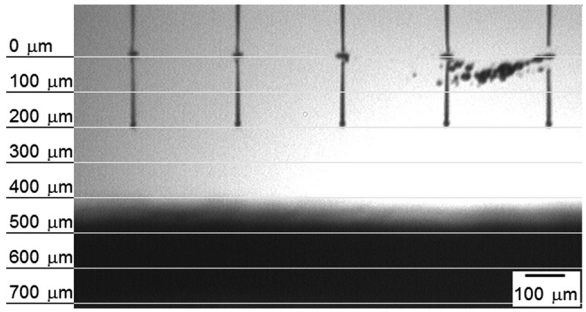

FIGURE 1 Formation of Vetbond n-butyl cyanoacrylate tissue adhesive drops by the piezoelectric inkjet printer. Reprinted from [17] with permission.

microscopy was performed using a Nanoscope IIIa Scanning Probe Microscope (Veeco Instruments, Santa Barbara, CA, USA); measurements were obtained in tapping mode. A Nano-Indenter XP instrument (MTS Systems, Oak Ridge, TN, USA) was used to examine the mechanical properties of inkjetted Vetbond tissue adhesive. The continuous stiffness measurement (CSM) technique was used to determine the elastic modulus (E) and the hardness (H) of the inkjetted material. The indentation depth was measured 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. The tests were performed at four different sites with a spacing of 1000 μm at a depth up to 500 nm on the surface of the Vetbond tissue adhesive. While the tip indents into the surface of the tested sample, the tip vibrates at a high frequency. In addition to measuring the indentation depth under the increasing load, a lock-in amplifier is used to measure the differentiation of loading force over the vertical displacement at the vibrating frequency during the indenting. This technique eliminates the need to examine the unloading process in order to obtain the slope of the unloading curve at the turning point. As a result, elastic modulus and hardness was determined continuously instead of at a discrete set of loads and depths. Recent Raman spectroscopy and attenuated total reflectance infrared spectroscopy studies by Wilson *et al.* have obtained complete bond conversion times for n-butyl cyanoacrylate of 38 and 41 minutes, respectively [18]. Nanoindentation studies were performed after the complete bond conversion time had elapsed. HAAE-1 human aortic endothelial cells were purchased from a commercial source (American Type Culture Collection, Manassas, VA, USA). The cells were examined for viability using the metabolic marker MTT assay

(3-[4,5-dimethyl-2-thiazol]-2,5-diphenyl-2H-tetrazolium bromide) [19]. HAAE-1 cells were seeded in well culture plates (~5000 cells/well) containing equal amounts of inkjetted Vetbond tissue adhesive ($n = 4$). Cells growing on empty wells with plain media were used as controls. At 24 hours, the cells were exposed to media (control) and assayed. The cells were incubated in a MTT medium (0.5 mg/mL) for 4 hours, the tetrazolium metabolized within the mitochondria was extracted, and the absorbance was quantified. The absorbance was determined spectrophotometrically at $\lambda = 550$ nm in an ELISA plate reader (Multiskan RC Labsystems, Helsinki, Finland).

RESULTS AND DISCUSSION

Vetbond tissue adhesive was successfully deposited into microscale patterns using the piezoelectric inkjet printer. Figure 2 shows an optical micrograph of a Vetbond tissue adhesive dot array pattern on a silicon wafer. Inkjetting of Vetbond tissue adhesive in dot array patterns on silicon (111) revealed ~56 μm features; spacing between drops was maintained at ~266 μm. The uniformity of pattern size and pattern spacing suggests reproducible positioning of material is provided by piezoelectric inkjet printing (Fig. 2). The Vetbond tissue

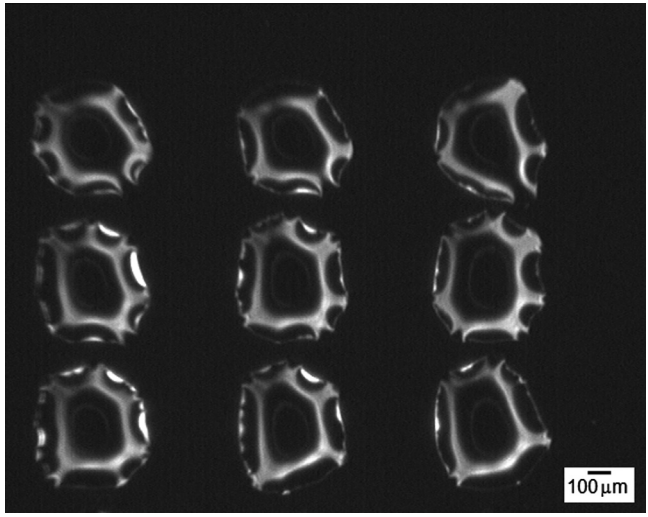

FIGURE 2 Optical micrograph of Vetbond n-butyl cyanoacrylate tissue adhesive inkjetted into an array pattern on a silicon substrate. Reprinted from [17] with permission.

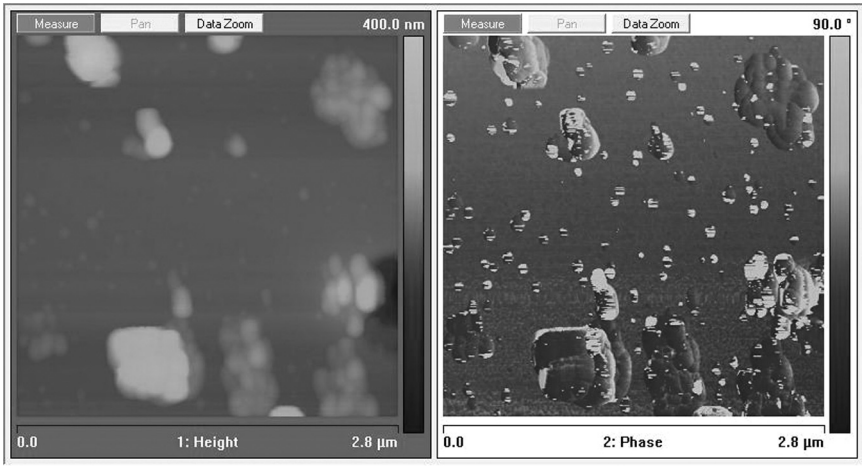

FIGURE 3 $2.8 \times 2.8\,\mu m$ topographic image of Vetbond n-butyl cyanoacrylate tissue adhesive inkjetted on a silicon substrate. (left) Z-scale of 400 nm and (right) phase image are shown.

adhesive produced reproducible features in commercial as-prepared form. This result indicates that piezoelectric inkjet printing may be directly used with conventional cyanoacrylate adhesives. Figure 3 contains atomic force micrographs of Vetbond tissue adhesive inkjetted in a thin film on a silicon (111) wafer. The micrographs revealed the presence of randomly oriented 2–3 μm globular structures. The average surface roughness (S_a) over the 20-μm scan-range was shown to be 0.117 μm; a root mean square (S_q) of 0.180 μm was observed. Figure 4(a) contains the average modulus of Vetbond tissue adhesive up to an indentation depth of 500 nm. Figure 4(b) contains the average hardness of Vetbond tissue adhesive up to an indentation depth of 500 nm. The elastic modulus values for inkjetted Vetbond tissue adhesive are significantly higher than Young's modulus values for 2-hydroxyethyl methacrylate and methacrylic acid obtained by microindentation testing (50–60 kPa) or by tensile testing (255 kPa) [20,21]. Differences in mechanical property values for these materials may result from differences in composition and viscoelastic behavior of the polymer. Figure 5 contains a graph illustrating MTT viability of HAAE-1 vascular endothelial cells for Vetbond tissue adhesive and media (control). Vetbond tissue adhesive showed lower viability than the control material. Chen *et al.* demonstrated that methoxypropyl cyanoacrylate and N-butyl cyanoacrylate exhibit cytotoxicity toward cultured bovine corneal epithelial cells, corneal endothelial cells, and

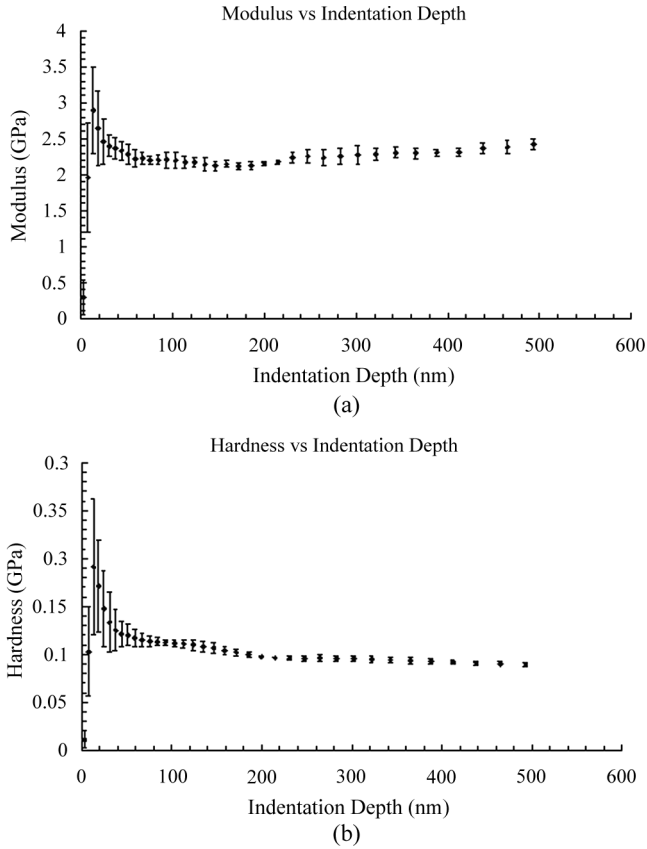

FIGURE 4 (a) Modulus *vs.* indentation depth of Vetbond n-butyl cyanoacrylate tissue adhesive. (b) Hardness *vs.* indentation depth of Vetbond n-butyl cyanoacrylate tissue adhesive. Data represented as mean ± standard deviation.

keratinocytes [22]. The toxicity of cyanoacrylate adhesives is attributed to the spontaneous degradation of this material into formaldehyde and cyanoacetate compounds; in particular, the release of formaldehyde may contribute to *in vitro* and *in vivo* cell toxicity [23,24]. *In vitro* kinetics studies by Leonard *et al.* demonstrated that N-butyl cyanoacrylate undergoes hydrolytic degradation at a relatively slow rate, which facilitates metabolism of cyanoacrylate degradation products by the surrounding tissues [25]. The degradation rate and toxicity of cyanoacrylate polymers can be reduced by increasing the length of the alkyl chain [26]. Inkjet printing and other novel micropatterning techniques may simultaneously improve the accuracy of cynaoacrylate

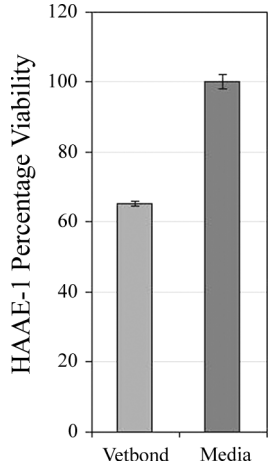

FIGURE 5 MTT viability of HAAE-1 vascular endothelial cells on Vetbond n-butyl cyanoacrylate tissue adhesive and media (control). Data represented as mean ± standard deviation.

use, reduce the amount of cyanoacrylate used in surgery, and decrease cytotoxicity [27].

CONCLUSIONS

Current methods for applying adhesives during microvascular surgery are considered to be rudimentary. We have demonstrated piezoelectric ink-jetting as a powerful, non-contact, and non-destructive technique for rapid prototyping of surgical sealants and biological adhesives for future clinical applications. Only sufficient material to form a seal will be introduced to the lesion site. As a result, toxicity may be minimized, bond lines between tissues may be reduced, and improved bond strengths may be realized. Piezoelectric jetting may overcome many of the problems associated with conventional tissue bonding materials and methods. We envision that this technique may be used to improve wound repair in microvascular surgery as well as in ophthalmic and orthopedic surgery.

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