PAPER DETAILS

TITLE: One Step Fabrication of Hollow and Highly Flexible Polydimethylsiloxane Microneedles

AUTHORS: Soner CAKMAK

PAGES: 219-224

ORIGINAL PDF URL: https://dergipark.org.tr/tr/download/article-file/2556573

Hittite Journal of Science and Engineering, 2022, 9 (3) 219–224
ISSN NUMBER: 2148–4171
DOI: 10.17350/HJSE19030000274

One Step Fabrication of Hollow and Highly Flexible Polydimethylsiloxane Microneedles

Soner Cakmak
Hacettepe University, Department of Bioengineering, Ankara, Turkey

ABSTRACT

In this study, the hollow and highly flexible polydimethylsiloxane microneedles were fabricated in a one step and simple design. For this purpose, a commercial dermastamping device (Dermastamp® 140 DRS) was used as a mold to obtain highly flexible PDMS microneedles containing channels. With the proposed design, microneedles with a total height of 1500 μm, 1500 μm center-to-center spacing and 150 μm channel diameter was successfully fabricated. These data are all compatible with the dimensions and the geometry of the mold used. Then, a syringe adapter was fabricated with a 3D printer and combined with the hollow PDMS microneedle patch for the high-throughput production of alginate beads. After the adapter and the hollow PDMS microneedle patch combination was placed into the syringe pump, the mostly spherical alginate beads with a mean diameter of 2.0 ± 0.3 mm was produced. To sum up, the proposed design and fabrication scheme first offer a novel and simple strategy for the fabrication of hollow polymeric microneedles. Moreover, this system has the potential to be used not only for the high-throughput microfluidic fabrication of polymeric beads, but also in controlled drug delivery systems and cell encapsulation studies.

Keywords:
Hollow microneedle; Microfabrication; One step; Polydimethylsiloxane; Alginate Beads.

Article History:
Received: 2022/07/25
Accepted: 2022/09/07
Online: 2022/09/28

Correspondence to: *Soner Cakmak*
Divison of Bioengineering, Hacettepe University, 06800 Ankara, Turkey
Tel: +90 312 297 6865
Fax: + 90 312 299 2157.
E-Mail:scakmak@hacettepe.edu.tr, sonercakmak@gmail.com

INTRODUCTION

Transdermal drug delivery systems offer an attractive and minimally invasive route where drug administration through oral or nasal ways is ineffective [1]. Conventional drug delivery system involves the injection of drugs into the skin via hypodermic needles with a length and diameter ranges of 8 – 50 mm and 0.05 – 2.7 mm ID, respectively [2]. However, hypodermic needle-mediated drug administration causes pain in patients and it is difficult to self-administration. In addition, there is a risk of blood-related contamination if re-used and accidental stinging [3]. To overcome these limitations, microneedle technology has been invented as a drug delivery system that can be administered painlessly and minimally invasively and is as effective as hypodermic needles. Microneedles are within the length of between 150 to 1500 µm and they can be used with the maximum patient comfort without inducing hypodermic needle associated problems [4]. Microneedles can be broadly classified into four categories: solid, coated, dissolving and hollow microneedles. Apart from the others, only hollow microneedles contain high-volume reservoirs in their structure, so that drugs can be sent to the body in a more controlled and desired dose than others. Moreover, thanks to the hollow structure and high reservoir capacity, they can also be used to extract blood and interstitial fluid for monitoring purposes [5-7], microfluidics applications [8, 9] and alginate bead encapsulated cell extrusion [10]. To date, there is no study has been found in the literature on the high-throughput production of polymeric beads using hollow microneedles.

Polymeric hollow microneedles were generally fabricated via lithography, etching, micromolding and additive manufacturing [11]. Due to the complexity of the fabrication methods used, hollow microneedles are accepted as the most difficult type of microneedle to manufacture. For example, a photomask is required and expensive devices are used in the lithographic fabrication. In addition, fabrication in this technique includes multiple successive steps such as deposition of a polymeric matrix onto a substrate, patterning via lithographic methods using a photomask and removal of uncrosslinked polymer resin [12, 13]. On the other hand, etching processing requires photomasking of a polymeric substrate and then, holes were created via plasma [14] or deep reactive ion [15] etchings. Besides, micromolds

are mainly used as replicas for the casting of polymeric solution or melts [16] or combined with other techniques given above [17, 18]. As mentioned earlier, this technique also involves laborious processes such as micromold preparation and subsequent integration with other techniques. In most of the studies done with additive manufacturing technology, stereolithography-based printing method is often adapted into the fabrication processes of hollow microneedles [9, 19, 20]. However, the materials used in this technique are limited to the biocompatible light-crosslinkable resins. For all these reasons, there is a great need for one-step, simple and inexpensive ways for the fabrication of hollow microneedles.

In this study, a one-step, simple method that can enable the use of many different polymers is proposed for the fabrication of hollow microneedles. For this purpose, a commercially available and height adjustable microneedle device containing a bundle of 140 stainless-steel needles, Dermastamp® 140 DRS, was used as the mold for the fabrication of hollow PDMS microneedles. The fabrication process started with i) preparation of PDMS and its curing agent preparation, ii) placing the Dermastamp® into the viscous PDMS solution, iii) obtaining solid form hollow microneedles by curing PDMS. Then, these microneedles were characterized by optical and scanning electron microscopes in terms of needle morphology, height and needle spacings. In the last part of the study, these developed microneedles were integrated into a syringe system and their usability in the high-throughput production of alginate beads was demonstrated as an example application.

MATERIALS AND METHODS

Materials

In order to prepare hollow microneedles, polydimethylsiloxane (PDMS) was purchased from Dow Corning Corporation, USA (Sylgard 184 silicone elastomer kit). For the fabrication of alginate beads, alginic acid sodium salt was received from Sigma (Germany) whereas calcium chloride ($CaCl_2$) and methylene blue were supplied from Merck (Germany) and Fluka (Germany), respectively. The distilled water was used for the preparation of alginate and methylene blue solutions.

One Step Fabrication of Hollow PDMS Microneedles

A commercially available microneedle device (Dermastamp® 140 DRS, Larcoboleno, South Korea) was used as a mold for the fabrication of hollow PDMS microneedles. Fig. 1a shows the detailed representation of the device and its apparatus. Dermastamp® 140 DRS is composed of 140 medical grade stainless- steel needles and the depth of the needles can be easily adjusted between 0.2 – 3.0 mm by its roller stick (Fig. 1a, i). It involves a tight-fitting plastic lid placed on the needle bundle in order to adjust the needle height. The diameter of the holes in the lower part of the plastic lid, where the needles enter, is 750 µm, and the diameter of the holes in the upper part, where they exit, is 400 µm (Fig. 1a, ii). The diameter of each needle is 150 µm, the length is 5 mm and the spacing between needles is 1.58 mm. After the needle bundle is locked by the plastic lid, a gap of 600 µm in the lower part and 250 µm in the upper part is formed between the solid stainless-steel needles and the holes in the plastic part (Fig. 1b). PDMS silicon base and its curing agent were mixed with a weight ratio of 10:1 and 8 g of PDMS was poured into a glass Petri dish (4 cm in diameter). The air bubbles were then degassed in a vacuum chamber and Dermastamp® device with needle heights set to 1 mm was immersed upside-down into the PDMS containing Petri dish (Fig. 1c). After the PDMS was cured at 80°C for 2 h in the spaces between the solid needles and the holes in the plastic part, the Dermastamp® was removed from the Petri dish. Then, the plastic lid was disassembled and hollow PDMS microneedles formed on the base of the solid needle bundle was carefully taken with a tweezer.
The size, length and morphology of the hollow PDMS microneedles were photographed via digital microscope (High Cloud, China). Moreover, their detailed characterization was also carried out via scanning electron microscope (SEM, Tescan GAIA3, Czech Republic).

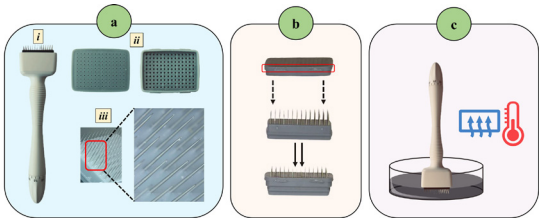

Figure 1. Fabrication steps of the hollow PDMS microneedles; (a) i: height adjustable commercially available microneedle device – Dermastamp® 140 DRS, ii: top and bottom photographs of the plastic lid; the diameter of the holes in the upper part is 400 µm, while the diameter of the lower parts is 750 µm, (b) the scheme representing the plastic lid tightly fits over the needle bundles; the area marked in red shows the wall thickness of the plastic lid, which determines the length of the microneedles and (c) the schematical representation of the thermally PDMS curing in the presence of Dermastamp® device.

Fabrication of Alginate Beads via Hollow PDMS Microneedles

Sodium alginate was dissolved in distilled water at a concentration of 1% (w/v). On the other hand, methylene blue was also prepared with a concentration of 10^{-3} M in distilled water in order to enhance the macroscopic visibility of the prepared alginate beads. Then, a few drops of methylene blue solution were transferred to alginate solution under constant shaking. A syringe adapter was designed and fabricated in order to test the usability of the hollow PDMS microneedles in the production of alginate beads. A bolt and nut type adapter was designed using AutoCad software (USA). Fig. 2a shows the 3-D

models of the adapter parts and their actual dimensions. Then, 3-D design was converted to .stl file available to 3-D printer (hamarad 3D printer, Turkey) and adapter parts were successfully printed using polylactic acid (PLA) filament. Using this design, microneedle patch can both be placed inside by its locking system or sticked to outside of the adapter. Fig. 2b shows the adapter tightly fitting to a syringe.

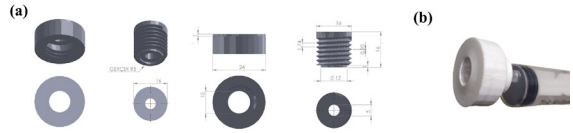

Figure 2. (a) Three-dimensional (3-D) design and (b) the final assembly of the syringe adapter used in the fabrication of microneedle-assisted alginate beads.

After the adapter was tightly inserted into the syringe, the hollow PDMS microneedle patch was carefully sticked around the outer hole of the adapter using a glue. Alginate solution containing methylene blue was transferred to the microneedle carrying syringe system and then this system was placed in a syringe pump (New Era Pump Systems, USA). The syringe pump was then fixed vertically on a plastic box. Afterwards, a 1.5 M of calcium chloride ($CaCl_2$) solution of was prepared and filled into a Petri dish. The alginate solution was extruded dropwise through a calcium chloride coagulation bath at a rate of 5 mL/min. The alginate beads were then imaged with an optical microscope (Olympus IX71, Japan), and the mean diameter and diameter distribution were calculated using these images with ImageJ software (NIH, USA).

RESULTS AND DISCUSSION

One Step Fabrication of hollow PDMS Microneedles

From the hollow microneedle fabrication perspective, various methods have been proposed in the literature for the fabrication of hollow microneedles in a simple and low-step manner. In some studies, hollow microneedles were prepared by first obtaining a master mold which is the replica of the final structure [17, 21, 22]. Then, polymer solutions or melts casted into the master mold form the hollow microneedles in desired macro/micro structures. However, the preparation of the master mold requires complex and laborious processes that make hollow microneedle fabrication difficult. Other studies involve approaches such as expensive laser systems both for rapid prototyping [23, 24] or hole opening [13], or post-lithography etchings [14, 25].

The fabrication scheme of the hollow PDMS microneedles used in this study is shown in Fig. 3. Herein, a relatively cheap Dermstamp device (~ $12) containing spaces between needle bundle and the plastic lid was used as a mold (Fig. 3a). After the Dermastamp device was immersed upside-down into the viscous PDMS solution, the spaces were filled with PDMS (Fig. 3b). Cured PDMS is not adhesive to most metallic or polymeric surfaces [26], and surfaces in contact with PDMS in our mold are metallic (stainless steel needle bundle) and polymeric (plastic lid - base holding the bundle) material. As a result, cured hollow PDMS microneedles were simply removed from the mold using a twizzer (Fig. 3d).

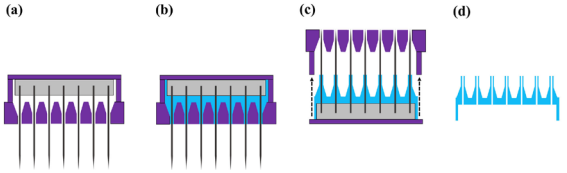

Figure 3. Schematic representation of the hollow PDMS microneedle fabrication. (a) Immersion of the Dermastamp® device into the viscous PDMS solution, (b) filling the cavities of the mold with PDMS, (c) removal of the plastic lid after PDMS was cured and (d) hollow PDMS microneedles formed.

The morphology of the hollow PDMS microneedles was investigated with a digital microscope and an SEM in detail as shown in Fig. 4a and b. Due to the mold geometry, hollow PDMS microneedles with tapered flange and cylinder tip like morphology was successfully produced (Fig. 4a and b; left column). Each microneedle had a total height of 1500 μm with a 1150 μm flange and 350 μm tip. The inner diameter of each channel passing through the microneedles are 150 μm similar to the diameter of the stainless-steel needles used as channel mold (Fig. 4a and b; middle column). Center-to-center spacing between each needle is calculated as 1500 μm (Fig. 4a and b; right column). These data are all compatible with the dimensions and the geometry of the mold used. Microneedles should have certain design parameters such as tip height, channel diameter or center-to-center spacing according to the application area used. In the case of drug delivery applications, microneedle height becomes a critical factor for pain management. Gill et al. showed that microneedles between 480 to 1450 μm height can reduce pain score 18 to 3-fold compared to 26 G needle in a human study [27]. If microneedles are to be used in blood sampling from the skin, their length must be at least 1450 μm to reach the deeper layer of the dermis [28]. Moreover, the channel diameters of the hollow microneedles for blood analysis should be at least 40 μm in order to provide good capillary penetration [29]. Hollow microneedles are frequently used for infusion of drugs into the skin at a certain flow rate and amount through their channels [30]. Therefore, drug infusion rate and amount are directly correlated with the channel diameter and the number of microneedles per row. With the fabrication method developed in this study, the microneedle height, channel diameter or number of microneedles per row can be easily adjusted by changing the mold properties such as wall thickness of the plastic lid, the diameter of the metal needles, or the number of metal needles in a bundle.

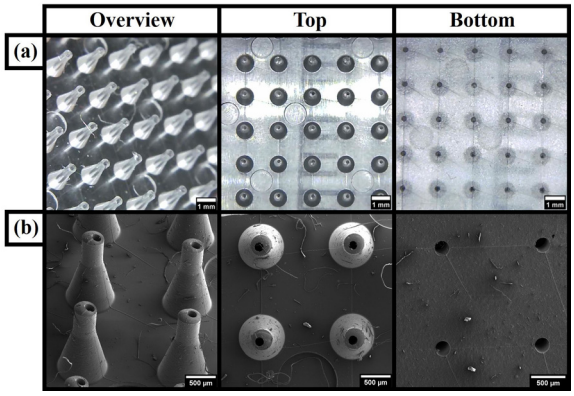

Figure 4. Overview, top and bottom images of the hollow PDMS microneedle patch captured by (a) digital microscope and (b) scanning electron microscope.

Fig. 5 shows the flexibility of the PDMS microneedles. As shown in Fig. 5a, b and c, hollow PDMS microneedle patches were bended in different axes in order to prove the flexibility of both patch base and microneedles, respectively. In both bending directions, patch base and microneedles returned to their initial state without any shape or mechanical deformation. The flexibility of the hollow PDMS patch is shown in detail in the supplementary movie (Movie S1. Flexibility of PDMS microneedles). Flexible PDMS materials have long been used for sensing, monitoring and microfluidics applications in the biomedical field due to their low cost, elastomeric structure, biocompatibility and ease of molding [31-33]. Therefore, hollow PDMS microneedle system developed in this study can be adapted to many biomedical applications with its easy one-step fabrication and high flexibility.

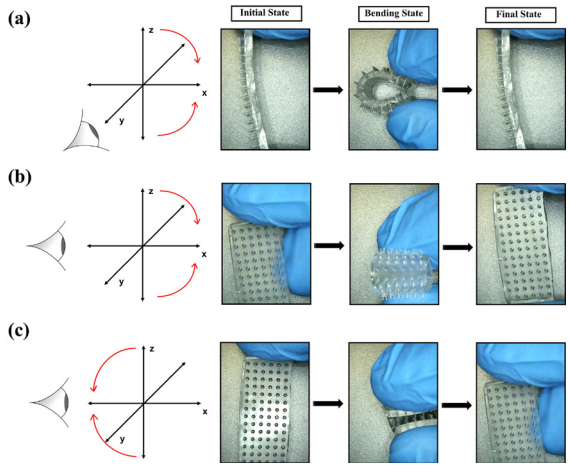

Figure 5. The photographs showing the flexibility of the hollow PDMS microneedle patch. The microneedle patch was all bended in the z – x plane but photographed from looking at (a) y and (b), (c) x axis.

Fabrication of Alginate Beads via Hollow PDMS Microneedles – An Application

Alginate is a natural polysaccharide extracted from brown algae. Thanks to their highly biocompatible, biodegradable and ease of fabrication properties, alginate beads are widely used as controlled drug delivery [34-36] and cell encapsulation vehicles [37, 38] and tissue engineering scaffolds [39]. Here in this work, the hollow PDMS microneedle system was used for the high-throughput fabrication of the alginate beads as an example study (Movie S2. Fabrication of alginate beads). The hollow PDMS microneedle patch was first connected to an adapter and glued to a syringe (Fig. 6a). The device was then placed to a syringe pump and alginate solution was extruded to calcium chloride solution (gelling agent) through hollow PDMS microneedles (Fig. 6b). Via this device, alginate beads with a mean diameter of 2.0 ± 0.3 mm was successfully produced (Figure 6c). The alginate beads had mostly spherical morphology with relatively narrow size distribution.

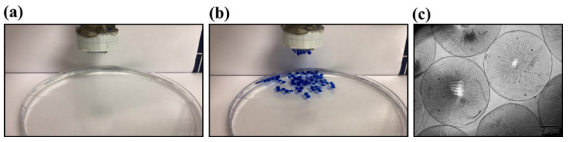

Figure 6. The photographs showing the hollow PDMS microneedle-assisted fabrication and final morphology of alginate beads; (a) before, (b) during fluid flow inside the microneedle channels and (c) optical microscopy images of the alginate beads.

CONCLUSION

In this study, a highly versatile hollow PDMS microneedle system was produced via one step fabrication method. In this way, an alternative model has been developed to the production difficulties encountered in hollow microneedle fabrication. These microneedles were composed of PDMS which makes them highly flexible. Here, they are used for high-throughput fabrication of alginate beads as an example study. Moreover, with this system, polymeric beads of different diameters and production rates can be easily produced simply by changing the microneedle diameter, number per row or solution flow rate. In addition, considering the originality of fabrication method developed and the microneedle system produced with it, this device can also be used in controlled drug delivery applications and cell encapsulation studies.

ACKNOWLEDGEMENTS

The author would like to thank Emrecan Yıldız and Buğra Kağan Ünal for their help in experimental studies.

CONFLICT OF INTEREST

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

REFERENCES

1. Prausnitz MR, Langer R. Transdermal drug delivery. Nature Biotechnology 26 (2008) 1261–1268. https://doi.org/10.1038/nbt.1504
2. Gill HS, Prausnitz MR. Does needle size matters?. Journal of Diabetes Science and Technology 1 (2007) 725–729. https://doi.org/10.1177/193229680700100517
3. Ingrole RSJ, Azizoglu A, Dul M, Birchall JC, Gill, HS, Prausnitz MR. Trends of microneedle technology in the scientific literature, patents, clinical trials and internet activity. Biomaterials 267 (2021) 120491 1–24. https://doi.org/10.1016/j.biomaterials.2020.120491
4. Waghule T, Singhvi G, Dubey SK, Pandey MM, Gupta G, Singh M, Dua K. Microneedles: a smart approach and increasing potential for transdermal drug delivery system. Biomedicine & Pharmacotherapy 109 (2019) 1249–1258. https://doi.org/10.1016/j.biopha.2018.10.078
5. Mukerjee EV, Collins SD, Isseroff RR, Smith RL. Microneedle array for transdermal biological fluid extraction and in situ analysis. Sensors and Actuators A 114 (2004) 267–275. https://doi.org/10.1016/j.sna.2003.11.008
6. Windmiller JR, Valdes-Ramirez G, Zhou N, Zhou M, Miller PR, Jin C, Brozik SM, Polsky R, Katz E, Narayan R, Wang J. Bicomponent microneedle array biosensor for minimally-invasive glutamate monitoring. Electroanalysis 23 (2011) 2303–2309. https://doi.org/10.1002/elan.201100361
7. Jiang X, Lillehoj PB. Microneedle-based skin patch for blood-free rapid diagnostic testing. Microsystems & Nanoengineering 6 (2020) 96 1–11. https://doi.org/10.1038/s41378-020-00206-1
8. Resnik D, Mozek M, Pecar B, Janez A, Urbancic V, Iliescu C, Vrtacnik D. In vivo experimental study of noninvasive insulin microinjection through hollow Si microneedle array. Micromachines 9 (2018) 40 1–17. https://doi.org/10.3390/mi9010040
9. Economidou SN, Uddin MJ, Marques MJ, Douroumis D, Sow WT, Li H, Reid A, Windmill JFC, Podoleanu A. A novel 3D printed hollow microneedle microelectromechanical system for controlled, personalized transdermal drug delivery. Additive Manufacturing 38 (2021) 101815 1–11. https://doi.org/10.1016/j.addma.2020.101815
10. Farias C, Lyman R, Hemingway C, Chau H, Mahacek A, Bouzos E, Mobed-Miremadi M. Three-dimensional (3D) printed microneedles for microencapsulated cell extrusion. Bioengineering 5 (2018) 59 1–26. https://doi.org/10.3390/bioengineering5030059
11. Carcamo-Martinez A, Mallon B, Dominguez-Robles J, Vora LK, Anjani QK, Donnely RF. Hollow microneedles: a perspective in biomedical applications. International Journal of Pharmaceutics 599 (2021) 120455 1–18. https://doi.org/10.1016/j.ijpharm.2021.120455
12. Wang PC, Wester BA, Rajaraman S, Paik SJ, Kim SH, Allen MG. Hollow polymer microneedle array fabricated by photolithography process combined with micromolding technique. Annual International Conference of the IEEE Engineering in Medicine and Biological Society (2009) 7026-709. doi: 10.1109/IEMBS.2009.5333317
13. Dardano P, De Martino S, Battisti M, Miranda B, Rea I, De Stefano L. One-shot fabrication of polymeric hollow microneedles by standard photolithography. Polymers 9;13(4):520 (2021) 1–13. doi: 10.3390/polym13040520
14. Bolton CJW, Howells O, Blayney GJ, Eng PF, Birchall JC, Gualeni B, Roberts K, Ashraf H, Guy OJ. Hollow silicon microneedle fabrication using advanced plasma etch technologies for applications in transdermal drug delivery. Lab on a Chip 20 (2020) 2788–2795. doi.org/10.1039/D0LC00567C
15. Li Y, Zhang H, Yang R, Laffitte Y, Schmill U, Hu W, Kaddoura M, Blondeel EJM, Cui B. Fabrication of sharp silicon hollow microneedles by deep-reactive ion etching towards minimally invasive diagnostics. Microsystems & Nanoengineering 5 (2019) 41 1–11. doi: 10.1038/s41378-019-0077-y
16. Khumpuang S, Ruther P, Paul O. Micromolding methods for hollow microneedle arrays using megasonically enhanced casting. TRANSDUCERS 2009 - 2009 International Solid-State Sensors, Actuators and Microsystems Conference, 2009, pp. 220-223, doi: 10.1109/SENSOR.2009.5285525
17. Wang P, Paik S, Kim S, Allen MG. Hypodermic-needle-like hollow polymer microneedle array: fabrication and characterization. Journal of Microelectromechanical Systems, vol. 23, no. 4, pp. 991-998, Aug. 2014, doi: 10.1109/JMEMS.2014.2307320
18. Mansoor I, Hafeli UO, Stoeber B. Hollow out-of-plane polymer microneedles made by solvent casting for transdermal drug delivery. Journal of Microelectromechanical Systems, vol. 21, no. 1, pp. 44-52, Feb. 2012, https://doi: 10.1109/JMEMS.2011.2174429
19. Szeto B, Aksit A, Valentini C, Yu M, Werth EG, Goeta S, Tang C, Brown LM, Olson ES, Kysar JW, Lalwani AK. Novel 3D-printed hollow microneedles facilitate safe, reliable, and informative sampling of perilymph from guinea pigs. Hearing Research 400 (2021) 108141 1–10. doi: 10.1016/j.heares.2020.108141
20. Rad ZF, Prewett PD, Davies GJ. Parametric optimization of two-photon direct laser writing process for manufacturing polymeric microneedles. Additive Manufacturing 56 (2022) 102953 1–14. https://doi.org/10.1016/j.addma.2022.102953
21. Perennes F, Marmiroli B, Matteucci M, Tormen M, Vaccari L, Di Fabrizio E. Sharp beveled tip hollow microneedle arrays fabricated by LIGA and 3D soft lithography with polyvinyl alcohol. Journal of Micromechanics and Microengineering 16 (2006) 473–479. doi:10.1088/0960-1317/16/3/001
22. Rad ZF, Prewett PD, Davies GJ. Rapid prototyping and customizable microneedle design: Ultra-sharp microneedle fabrication using two-photon polymerization and low-cost micromolding techniques. Manufacturing Letters 20 (2021) 39–43. https://doi.org/10.1016/j.mfglet.2021.10.007
23. Trautmann A, Roth GL, Nujiqi B, Walther T, Hellmann R. Towards a versatile point-of-care system combining femtosecond laser generated microfluidic channels and direct laser written microneedle arrays. Microsystems & Nanoengineering 5 (2019) 6 1–9. doi: 10.1038/s41378-019-0046-5
24. Li R, Liu X, Yuan X, Wu S, Li L, Jiang X, Li B, Jiang X, Gou M. Fast Customization of Hollow Microneedle Patches for Insulin Delivery. International Journal of Bioprinting 8(2) (2022) 124–135. doi: 10.18063/ijb.v8i2.553
25. Wu T, You X, Chen Z. Hollow Microneedles on a Paper Fabricated by Standard Photolithography for the Screening Test of Prediabetes. Sensors (Basel). 22(11) (2022) 4253 1–11. doi: 10.3390/s22114253
26. Ye X, Cai D, Ruan X, Cai A. Research on the selective adhesion characteristics of polydimethylsiloxane layer. AIP Advances 8 (2018) 095004 1–8. https://doi.org/10.1063/1.5041867
27. Gill HS, Denson DD, Burris BA, Prausnitz MR. Effect of microneedle design on pain in human volunteers. The Clinical Journal of Pain 24(7) (2008) 585-594. doi: 10.1097/AJP.0b013e31816778f9
28. Chaudhri BP, Ceyssens F., de Moor P, van Hoof C, Puers R. A high aspect ratio SU-8 fabrication technique for hollow microneedles for transdermal drug delivery and blood extraction. Journal of Micromechanics and Microengineering 20 (2010) 064006 1–6. doi:10.1088/0960-1317/20/6/064006
29. Zhou R, Chang HC. Capillary penetration failure of blood

suspensions. Journal of Colloid and Interface Science 287 (2005) 647–656. doi: 10.1016/j.jcis.2005.02.023. PMID: 15925633
30. Kim YC, Park JH, Prausnitz MR. Microneedles for drug and vaccine delivery. Advanced Drug Delivery Reviews 64 (2012) 1547–1568. doi: 10.1016/j.addr.2012.04.005
31. McDonald JC, Duffy DC, Anderson JR, Chiu DT, Wu H, Schueller OJ, Whitesides GM. Fabrication of microfluidic systems in poly(dimethylsiloxane). Electrophoresis 21 (2000) 27–40. doi: 10.1002/(SICI)1522-2683(20000101)21:1<27::AID-ELPS27>3.0.CO;2-C
32. Sia SK, Whitesides GM. Microfluidic devices fabricated in poly(dimethylsiloxane) for biological studies. Electrophoresis 24 (2003) 3563–3576. https://doi.org/10.1002/elps.200305584
33. Raj M K, Chakraborty S. PDMS microfluidics: A mini review. Journal of Applied Polymer Science 137(27) (2020) 48958 1–14
34. Murata Y, Sasaki N, Miyamoto E, Kawashima S. Use of floating alginate gel beads for stomach-specific drug delivery. European Journal of Pharmaceutics and Biopharmaceutics 50 (2000) 221–226. doi: 10.1016/s0939-6411(00)00110-7
35. Rashidzadeh B, Shokri E, Mahdavinia GR, Moradi R, Mohamadi-Aghdam S, Abdi S. Preparation and characterization of antibacterial magnetic-/pH-sensitive alginate/Ag/Fe3O4 hydrogel beads for controlled drug release. International Journal of Biological Macromolecules 154 (2020) 134–141. https://doi.org/10.1016/j.ijbiomac.2020.03.028
36. Armutcu C, Piskin S. Evaluation of controlled hydroxychloroquine releasingperformance from calcium-alginate beads. Hittite Journal of Science and Engineering 8(3) (2021) 255–263. DOI: 10.17350/HJSE19030000236
37. Zhou H, Xu HH. The fast release of stem cells from alginate-fibrin microbeads in injectable scaffolds for bone tissue engineering. Biomaterials 32 (2011) 7503–7513. doi: 10.1016/j.biomaterials.2011.06.045
38. Zeng Q, Han Y, Li H, Chang J. Bioglass/alginate composite hydrogel beads as cell carriers for bone regeneration. Journal of Biomedical Materials Research Part B Applied Biomaterials. 102B (2014) 42–51. doi: 10.1002/jbm.b.32978
39. Agarwal T, Kabiraj P, Narayana GH, Kulanthaivel S, Kasiviswanathan U, Pal K, Giri S, Maiti TK, Banerjee I. Alginate bead based hexagonal close packed 3d implant for bone tissue engineering. ACS Applied Materials & Interfaces 8 (2016) 32132–32145. DOI: 10.1021/acsami.6b08512