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Development of cup shaped microneedle array for transdermal drug delivery

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Microneedle technology is one of the attractive methods in transdermal drug delivery. However, the clinical applications of this method are limited owing to: complexity in the preparation of multiple coating solutions, drug leakage while inserting the microneedles into the skin and the outer walls of the solid microneedle can hold limited quantity of drug. Here, the authors present the fabrication of an array of rectangular cup shaped silicon microneedles, which provide for reduced drug leakage resulting in improvement of efficiency of drug delivery and possibility of introducing multiple drugs. The fabricated solid microneedles with rectangular cup shaped tip have a total height of 200 μm. These cup shaped tips have dimensions: 60×60 μm (length $\times$ breadth) with a depth of 60 μm. The cups are filled with drug using a novel in-house built drop coating system. Successful drug dissolution was observed when the coated microneedle was used on mice. Also, using the above method, it is possible to fill the cups selectively with different drugs, which enables simultaneous multiple drug delivery. © *2015 American Vacuum Society*. [http://dx.doi.org/10.1116/1.4919779]

I. INTRODUCTION

There are many drug delivery methods available such as oral, transmucosal, and transdermal. Among all these methods, transdermal drug delivery is the most preferred method, due to its high efficiency and less side effects.[1,2] However, using this method, it is difficult to deliver protein, vaccine, gene, and antibody based drugs because of their high molecular size and charge issues.[3] Several possible approaches have been proposed to overcome these limitations. In particular, they are divided into two classes, namely, passive and physical methods. In the passive method, in order to increase the drug permeability through the skin, researchers have tried chemical penetration enhancers and thermodynamic activity control.[4] Whereas in the physical method, increase of drug permeability through skin was achieved using ultrasound, iontophoresis, electroporation, and microneedles.[4] Among these approaches, the microneedle approach is considered as one of the best methods to deliver the drug molecules through the skin.[4–6]

Different types of microneedle technologies have been reported for transdermal drug delivery.[7] Among them, solid and hollow microneedle technologies have been studied intensively.[7–13] In the case of hollow microneedles, the quantity of drug delivery into the body needs to be controlled using an external pump or syringe. Hence, it can be used in continuous delivery of drug such has insulin, etc. Whereas in case of solid microneedles, three different modes of drug delivery have been proposed, namely: (1) Poke and patch approach, (2) poke and release approach, and (3) coat and poke approach.[14,15] Among all these approaches, coat and poke approach has gained higher acceptability.[12] In this

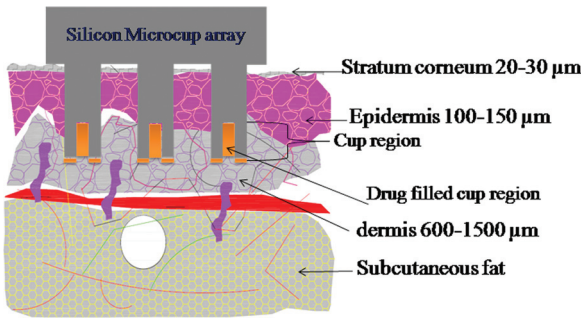

FIG. 1. Cross section of human skin inserted with cup shaped solid microneedles containing drug in the cup regions.

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approach, the fabricated solid microneedles will be coated with drug and inserted into the skin for successive dissolution of the coated drug. Figure 1 shows the cross section of the human skin inserted with solid microneedles. In this Fig. 1, it can be seen that the outermost stratum corneum layer thickness is 20–30 μm. The subsequent layers are epidermis and dermis whose thicknesses are in the range of 100–150 and 600–1500 μm, respectively. The above mentioned skin layers impose constraints for the design of the microneedle length for successful drug delivery. Hence, to ensure painless and leak proof transdermal drug delivery, microneedles have to penetrate to a depth of 150–200 μm.[16]

Several research groups have reported on the realization of different shaped solid microneedles using different materials (Table I). Chabri *et al.*, Kalluri *et al.*, DeMuth *et al.*, and Matriano *et al.* have fabricated solid microneedles of pyramid shape using silicon (Si), stainless steel (SS), and polymer and titanium, respectively. In all these cases, the drug was coated on the outer walls of microneedles.[10,17–19] It is likely that, due to skin shear force, the coated drug on the outer wall might get wiped off while inserting the microneedles into the skin. Also, the quantity of drug coated on the outer walls will be less. To overcome these disadvantages, Han *et al.* and Gill and Prausnitz have fabricated the grooved and pocketed microneedles using polymer and stainless steel, respectively.[20,21] However, by using these solid microneedle structures also, it was difficult to control the quantity of drug that needs to be coated on the outer wall of the same. Also, in these methods, the quantity of drug to be delivered will be less, thus requiring a large area array of microneedles or multiple insertions.

Keeping the above aspects in mind, in our present study, we have fabricated cup shaped Si microneedles wherein (in the cup region) the drug molecules can be filled conveniently (Fig. 1). Thus, coated/filled drug in the cup regions will not get wiped off while inserting the solid microneedles into the skin. It is to be noted that, as reported in the earlier literature,[7] the solid microneedles were coated by dipping or spraying methods[7] due to which the drug loss will be relatively high and also each microneedle in an array will be coated with different thicknesses.[14] Therefore, we have adopted a different method, i.e., the drop coating method, which enabled to fill the microcup regions with drug in a controlled manner.

In this paper, we present the design and fabrication of cup shaped solid Si microneedle array using lithography and deep reactive ion etching (DRIE) process. The mechanical stability of the microneedle array was evaluated using micro-universal testing machine (μUTM). The microneedle array was packaged in band-aid and its mechanical stability as well as ease of usage was demonstrated on a human volunteer. The fabricated microcup shaped solid microneedles arrays were filled with model drug using in-house built dedicated drop coating setup. The drug filled cup shaped microneedles were inserted into mice skin and drug dissolution was confirmed using fluorescence imaging technique.

TABLE I. Different shaped solid microneedles.

Author	Solid microneedles material	Shape of solid microneedles
Chabri *et al.* (Ref. 17)	Si	Pyramidal
Kalluri *et al.* (Ref. 18)	SS	Pyramidal
DeMuth *et al.* (Ref. 10)	Polymer (PLGA)	Pyramidal
Matriano *et al.* (Ref. 19)	Titanium	Pyramidal
Han *et al.* (Ref. 20)	Polymer	Grooved
Gill *et al.* (Ref. 21)	SS	Pocketed

II. EXPERIMENT

A. Fabrication of flat tip microcup

In our work, we have employed two-step lithography process for the realization of cup shaped solid microneedles. Figure 2(a) shows the graphical illustration of the steps followed in the fabrication process. Initially, a 4 in. Si wafer was cleaned in piranha solution for 15 min as shown in step 1. After cleaning, the AZ4562 photoresist (PR) was coated on to the Si wafer as shown in step 2. After coating, first lithography process was carried out to obtain microcup regions. A 60×60 μm mask structure was used to obtain the microcup structure; the pattern for the cup region is shown in step 3. The developed (using AZ developer) structure after the lithography process is shown in step 4. Subsequently, the exposed Si was etched to a depth of 60 μm using DRIE process (Bosh process with 15 μm min^{-1} recipe was used) as shown in step 5. Finally, the protected PR on the microcup regions was removed by dipping the sample in an acetone solution as shown in step 6. Further, the second lithography process was carried out to obtain the pillar structures (solid microneedles). To obtain these structures, again a PR was coated on to the fabricated cup structures as shown in step 7. Here, the AZ4562 photoresist was coated to mask microcup and microneedle pillar regions. After coating, masking and exposing was carried out as shown in step 8. After exposer, the patterning was carried out using AZ developer solution; the resulting structures are shown in step 9. Care was taken during the exposing and patterning to protect the cup and pillar positions with proper alignment. After patterning, the exposed Si was etched to a depth of 200 μm using DRIE process as shown in step 10. Finally, the protected PR on the microcup and micropillar regions was removed by dipping the sample in acetone as shown in step 11. Scanning electron microscope image (SEM) of the fabricated microcup structure is shown in Figs. 3(a) and 3(b).

B. Fabrication of tapered tip microcup

Fabricated cup shaped solid microneedles using the above mentioned process does not have tapered tip to facilitate easy penetration into the skin. The microneedle without the tapered end requires more force to penetrate into the skin. To overcome this drawback, tapered tip microneedles have been fabricated using isotropic etching (15 μm min^{-1} undercut and 15 μm min^{-1} deep etch recipe is used). Subsequent to step 9 of Fig. 2(a), 1 min isotropic etching [as shown in

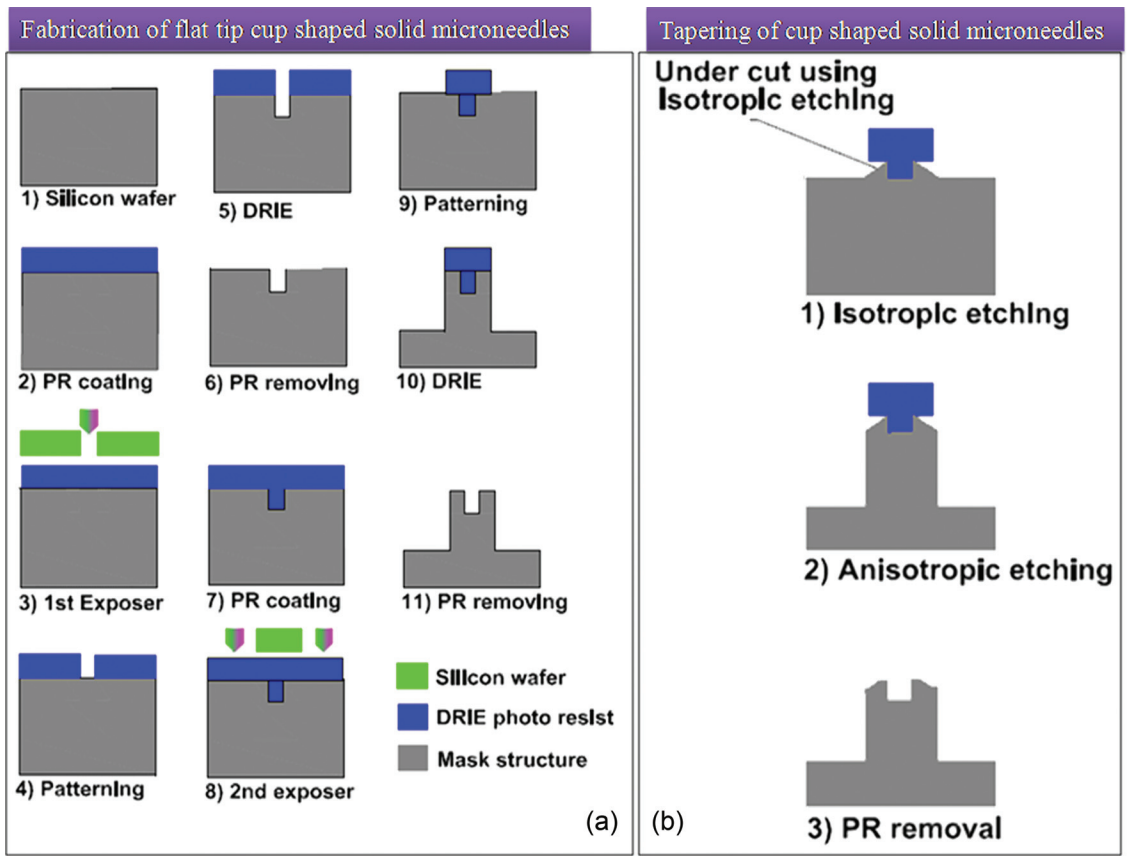

FIG. 2. (a) Process flow for the fabrication of out-of-plane array of cup shaped solid microneedles. (b) Process flow to fabricate tapered tip out-of-plane array of cup shaped solid microneedles.

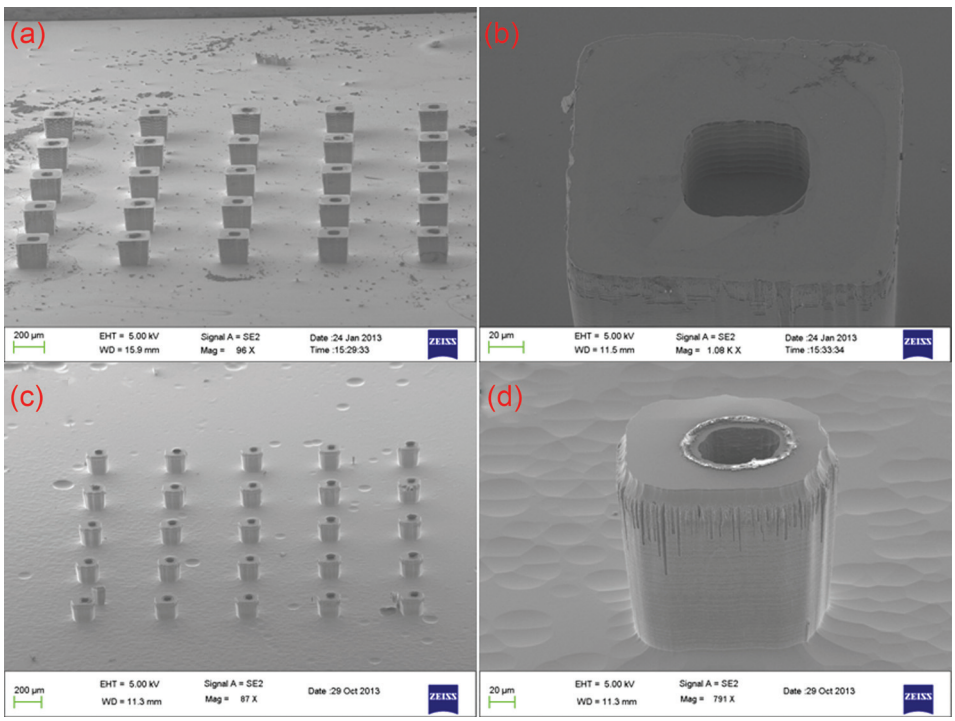

FIG. 3. SEM image of microcup shaped solid microneedles. (a) An array of flat tip cup shaped solid microneedles. (b) Single flat tip cup shaped solid microneedles. (c) An array of tapered tip cup shaped solid microneedles. (d) Single tapered tip cup shaped solid microneedles.

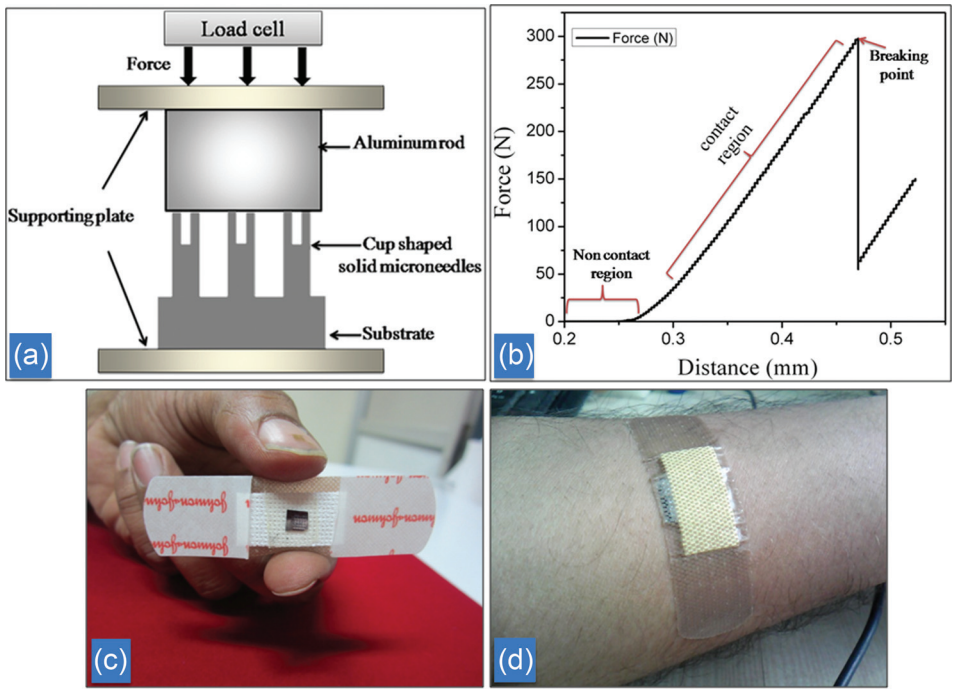

FIG. 4. (a) Schematic of the microneedles failure mechanism analysis. (b) Measured load–displacement curve for the microneedle. (c) Microneedle embedded in commercially available band-aid. (d) Human volunteer was successfully applied the microneedle patch on to his forearm.

step 1 of Fig. 2(b)] was carried out to achieve tapered tip. This was followed by anisotropic etching to obtain desired height microneedles [as shown in step 2 of Fig. 2(b)]. The top PR on the microcup region was removed by dipping the sample in acetone as shown in step 3 of Fig. 2(b). Finally, the fabricated tapered tip microcups are shown in Figs. 3(c) and 3(d). In order to make them biocompatible and hydrophilic the fabricated microcup structures were coated with SiO_2 (1 μm thermal oxidation). This results in good adhesion of the drug on to microcups.

C. Mechanical strength of the microneedles

The fabricated tapered tip cup shaped Si microneedles were subjected to vertical load in order to study their mechanical stability. The μUTM (Mecmesin: MultiTest 10-i) was used to estimate the breaking force of the microneedles. The schematic of the experimental setup used for this purpose is shown in Fig. 4(a). As can be seen, the cup shaped solid microneedles were mounted on the supporting plate. After proper alignment, the load cell was brought in contact with the microneedles and moved slowly at a speed of 2.5 μm ms^{-1} until it caused breaking of the microneedles. The resulting breaking force was recorded. Figure 4(b) shows the variation of measured breaking force versus displacement. Also, the mechanical stability was estimated by inserting the microneedle array into human volunteer's skin, as shown in Figs. 4(c) and 4(d) (human experiment was approved by the Institutional Ethics Committee, Indian Institute of Science, Bangalore, India, and carried out according to institutional guidelines). Before insertion, the microneedle patch was placed on to a standard band-aid structure using double sided tape for ease of usage.

D. Preparation of coating solution

Aqueous viscous coating solution was prepared to fill the microcup regions. The solution was prepared using deionized water along with the carboxymethylcellulose as a viscosity enhancer (20 mg/ml) at room temperature and insulin was used as a model drug. The fluorescent agent was added to the coating solution for the convenience of observing the drug release.

E. Drug filling on to the microcups

Initially, the fabricated microneedle array was cleaned in 50:50 mixtures of deionized water and isopropyl alcohol at room temperature for 30 min. Drop coating method was used to fill the microcup regions with the necessary drugs, as shown in Fig. 5(a). It can be seen that, the micropipette with 10 μm tip diameter was used to drop the drug droplet into the microcup regions. The micropipette was connected through silicone tube to the syringe pump containing the coating solution (model drug + viscosity enhancer + fluorescent agent). To fill up the drugs into the microcup regions, the fabricated microcup array was placed on the X-Y stage. Hence, the drug can be filled into each microcup region easily just by moving X-Y stage. Along with the X-Y stage, Z axis movement was also used, to drop the drug exactly into the cup region. Drug filling using Z-axis movement is schematically illustrated in Fig. 5(b). By observing through optical microscope, the micropipette position was initially aligned to the microcup region using X-Y stage movement

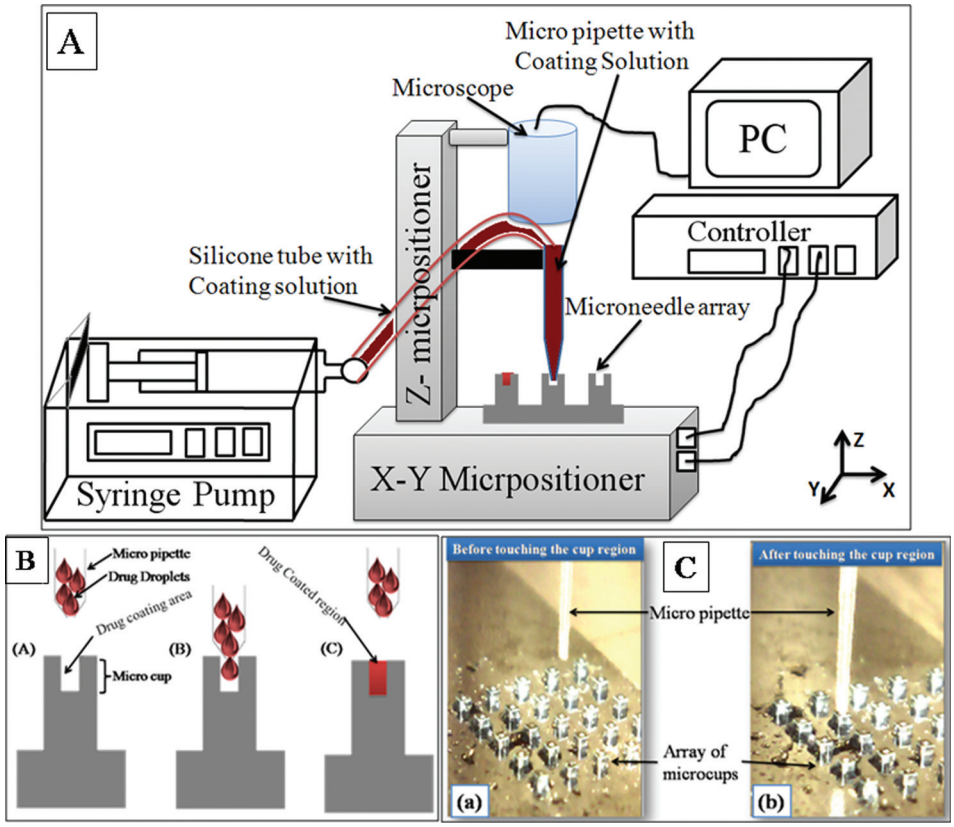

FIG. 5. (A) Schematic of drop coating system showing X, Y, and Z-micropositioner along with microscope, syringe pump, and computer to control the micropositioner and to observe the alignment of coating process. (B) Schematic of the coating process. (a) Micropipette tip aligned to fill up the drug. (b) Micropipette is moved close to the cup region (using Z-axis movement) and formed a drug drop let to release into cup region. (c) After releasing the drug drop the cup region will be filled with the drug and the micropipette was moved back to its original position. (C) Microscopic image of the drop coating method. (a) The micropipette is aligned to cup region to fill up the drug. (b) After alignment the micropipette was moved toward the microneedles array to fill up the drug into the cup region.

[see Fig. 5(C-a)]. After proper alignment, the glass micropipette was made to move toward microcup region using Z-axis movement [see Fig. 5(C-b)]. The drug droplet was formed using syringe pump until it touches and releases into the cup position. After releasing the droplet or filling the cup region, the micropipette was made to move to its original position using Z axis movement. Similarly, other microcup regions were also filled by repeating the same procedure and by moving the X-Y stage accordingly (the distance between the two adjacent microcups was 600 μm). (Video is attached in the supplementary material.[22])

F. Animal trial

Female nude mice (Nude HSD-Fox N1) of 6–8 weeks age, weighing between 18 and 22 g, were used in this study. All mice were housed under specific pathogen-free conditions and maintained in individually ventilated cages. Temperature ($22 \pm 2\,^{\circ}$C) and humidity ($50\% \pm 10\%$) were kept constant with a 12-h light/dark cycle, and mice had access to standard laboratory chow and water ad libitum. Animal experiments were approved by the Institutional Animal Ethics Committee, Indian Institute of Science, Bangalore, India and carried out according to institutional guidelines for animal care and use.

All the experimental animals were anesthetized appropriately by using anesthetic agents such as Ketamine and Xyazine before conducting the experiments. The drug filled microneedles were manually inserted in the dorsal region of the animal body. The patch was retained in place for 60 min and subsequently removed to observe the fluorescence dissolution from the cup region.

III. RESULTS AND DISCUSSION

It is a known fact that the drug coated on the outer walls of the conventional solid microneedle will get wiped off while inserting microneedles into the skin.[7] Also, the drug coated near the base region will not deliver effectively into the skin, since the microneedle base will not penetrate deep into the skin.[23] Due of these reasons, the drug leakage will be common in traditional (pyramidal shaped) solid microneedles. Hence, Gill and Prausnitz[21] and Han *et al.*[20] have proposed grooved and pocketed microneedles to reduce the drug leakage while inserting (coated drug stays on the skin surface) and to increase the drug quantity. To address the similar issue, in our present work, an array of cup shaped solid microneedles were successfully fabricated using conventional microfabrication technique [Figs. 3(a) and 3(b)]. Using this design, the coated/filled drugs in the cup regions

will not be wiped off while inserting the solid microneedles into the skin. Moreover, in our subsequent experiments, tapered tip solid microneedles were fabricated using isotropic etching process [as shown in Figs. 3(c) and 3(d)], which enables easy insertion of the microneedles in to the skin. The total height and width of the fabricated cup shaped solid microneedles are 200 and 150 μm, respectively. The depth of the cup structures on the solid microneedle is of 60 μm. By using this structure, it is possible to fill 0.216 nl quantity of drug into a single microcup, and in total 5.4 nl of drug for the entire 5×5 arrays. The quantity of drug to be filled can be varied by selecting suitable number of microneedles in the array.

The mechanical stability of the fabricated cup shaped solid microneedles was estimated using μUTM. The variation of the load–displacement as measured using μUTM is shown in Fig. 4(b). As can be seen, initially the microneedle is not in contact with the load cell. The load cell is made to move toward microneedles sample until it touches the microneedle tip. Further, continued movement of the load cell results in pressing the microneedle array (and hence applying the load) until all the needles break. This is the ultimate breaking load for the microneedle array. The observed ultimate breaking load [discontinuity in Fig. 4(b)] for the solid microneedle array is found to be ~49 MPa, which is well above the skin resistive force (~3.18 MPa).[24] In addition, bed-of-nail effect is one of the most important considerations while inserting an array of structures into a tissue. In order to check the bed-of-nail effect, the fabricated microneedles were inserted into a medium hard silicone rubber and observed the insertion marks (microscopically) on the silicone rubber. These marks showed that the fabricated microneedles with 500 μm pitch are good enough to avoid the bed-of-nail effect. To make the microneedle array as user friendly for easy insertion, the microneedle array was sterilized and embedded into band-aid like structure [Fig. 4(c)]. This generally facilitates self insertion, without the need of any experts. The band-aid containing the microneedles applied by the volunteer himself onto his forearm successfully is shown in Fig. 4(d). After some time, the band-aid was removed and it was confirmed that all 25 microneedle in the array were present intact. It was noted that the volunteer experienced very less pain during the insertion of microneedles. Also, there was no breakage in any of the microneedles during insertion. This confirms the good mechanical stability of the fabricated microneedles for insertion into the human skin. However, at this stage, human trials were restricted only to study the mechanical stability of microneedles.

In most of the earlier reports, the drug coating onto the microneedles was done using dip coating method.[14] Using dip coating method, it is difficult to select the area to be coated. Therefore, Gill and Prausnitz have presented the microneedle coating using row-coating device. By using this system, it was possible to coat only in-plane microneedles. Also, coating of different drugs on to each microneedle will be difficult.[21] Hence, in our present study, an improved version of the drug filling system was developed to coat/fill drug into the fabricated cup shaped solid microneedles and the same is schematically shown in Figs. 5(A) and 5(B). The microscopic image of the drug filling step is shown in Fig. 5(C). It is important to note that, using our presently developed drug coating system, it is easy and effortless to fill drugs on to the out-of-plane cup shaped solid microneedles. Additionally, it also enables to have a good control on the quantity of drug to be filled.

The drug coated microcup structure is shown in Fig. 6(c). The coated microneedle array was placed on to the band-aid structure using double sided tape to make it easy and more convenient for usage [Fig. 6(a)]. The band-aid containing microneedle was manually applied on to the mice skin, as shown in Fig. 6(b). After 60 min, the inserted microneedle array (band-aid) was removed from the mice and reduction in the fluorescence emission confirms the dissolution of filled drug [Fig. 6(d)]. On the other hand, it was observed that there was no any dye mark left on the mice skin surface. This confirms the leak proof drug delivery using the presently developed cup shaped solid microneedles.

Some of the therapeutic delivery scenarios may require the application of multiple drugs from the same microneedle array. To address this scenario, our next objective is to coat multiple drugs on to the same microneedles array without any drug-to-drug interactions/interference. Gill and Prausnitz have demonstrated the multiple drug coating on to the pocketed solid microneedles using liquid glycerol method. They coated three pockets on the microneedle with three different dyes, by several dipping and washing steps.[23]

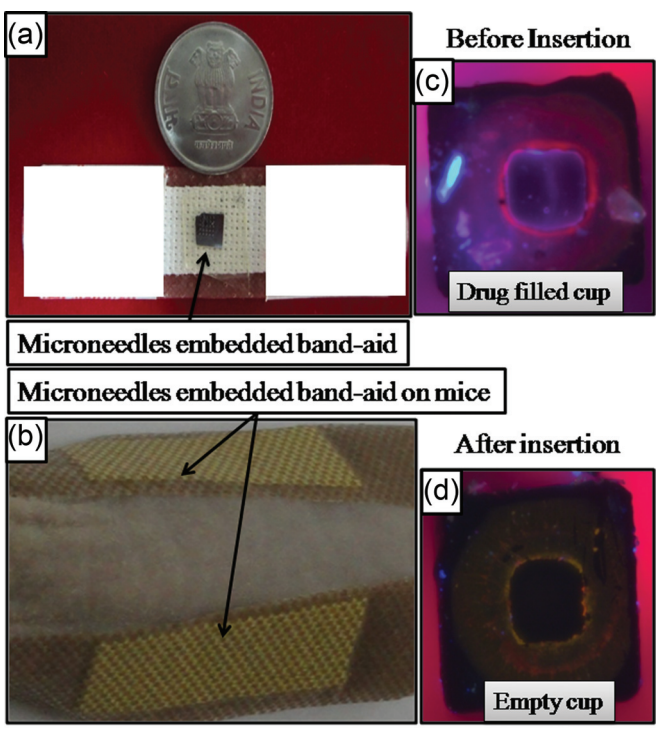

FIG. 6. (a) Microneedles embedded in band aid. (b) Microneedles embedded band aid was applied on to the mice skin. (c) Fluorescence image of the drug filled cup shaped microneedle. (d) Microneedle after removing from the mice skin, drug coated inside the cup region is completely dissolved (reduced fluorescence emission).

As can be noticed, this method requires multiple steps. Usage of this coated microneedle may lead to a cross contamination between each drug molecules. These drug coated pockets on the microneedle were located at different positions from the tip of the microneedle. As a result, the drug release into the subject took place at different times. However, by using our presently developed cup shaped microneedles, it is possible to deliver multiple drugs at the same time, without causing any drug to drug interactions. Also, the dedicated drop coating system developed in the present work is convenient and effortless to coat multiple drugs onto the microcup structures.

In our present work, one of the observations made is that the region of the substrate between the two adjacent microneedles will also get coated along with the microcup region. It is due to the difficulty of controlling the drug drop size coming out from the micropipette. The possible solutions for the above mentioned limitation are as follows: (1) by functionalizing the microcup region, (2) by preparing high viscous coating solutions, (3) by controlling the drug drop size, and (4) by using proper pumping mechanism to pump the drug through micropipette. This work is in progress.

IV. CONCLUSIONS

In conclusion, we have designed and successfully fabricated the cup shaped solid Si microneedle array. Application of cup shaped microneedles for leak proof and controlled drug delivery has been demonstrated. In order to reduce the insertion force, the microneedle tip tapering was done using isotropic etching process. SiO_2 was coated on to the fabricated microneedles to make them hydrophilic. The drug filling into the cup regions was carried out successfully using a dedicated in-house built drop coating system. The proposed method of using cup shaped microneedles helps in quantitative estimation of the drug thereby enabling controlled drug delivery with minimum leakage/losses. Also, multiple drugs filling on to the same microneedle array was explored by using this drop coating system. Finally, the drug coated microneedles were successfully inserted on to a mice skin, and the drug dissolution has been studied. A complete transfusion of drug into the skin has been observed.

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[1]M. R. Prausnitz, S. Mitragotri, and R. Langer, Nat. Rev. Drug Discovery **3**, 115 (2004).
[2]M. R. Prausnitz and R. Langer, Nat. Biotechnol. **26**, 1261 (2008).
[3]H. Kalluri and A. Banga, AAPS PharmSciTech **12**, 431 (2011).
[4]J. Hadgraft and M. E. Lane, Phys. Chem. Chem. Phys. **13**, 5215 (2011).
[5]C. Pegoraro, S. MacNeil, and G. Battaglia, Nanoscale **4**, 1881 (2012).
[6]Z. Xiang, H. Wang, A. Pant, G. Pastorin, and C. Lee, Biomicrofluidics **7**, 026502 (2013).
[7]Y.-C. Kim, J.-H. Park, and M. R. Prausnitz, Adv. Drug Delivery Rev. **64**, 1547 (2012).
[8]K. B. Vinayakumar, G. M. Hegde, M. M. Nayak, N. S. Dinesh, and K. Rajanna, Microelectron. Eng. **128**, 12 (2014).
[9]P. C. DeMuth, Y. Min, B. Huang, J. A. Kramer, A. D. Miller, D. H. Barouch, P. T. Hammond, and D. J. Irvine, Nat. Mater. **12**, 367 (2013).
[10]P. C. DeMuth, X. Su, R. E. Samuel, P. T. Hammond, and D. J. Irvine, Adv. Mater. **22**, 4851 (2010).
[11]L. M. Strambini, A. Longo, A. Diligenti, and G. Barillaro, Lab Chip **12**, 3370 (2012).
[12]Z. Wei *et al.*, Lab Chip **14**, 4093 (2014).
[13]Z. Xiang *et al.*, Biomicrofluidics **7**, 066501 (2013).
[14]K. van der Maaden, W. Jiskoot, and J. Bouwstra, J. Controlled Release **161**, 645 (2012).
[15]T.-M. Tuan-Mahmood, M. T. C. McCrudden, B. M. Torrisi, E. McAlister, M. J. Garland, T. R. R. Singh, and R. F. Donnelly, Eur. J. Pharm. Sci. **50**, 623 (2013).
[16]A. Arora, M. R. Prausnitz, and S. Mitragotri, Int. J. Pharm. **364**, 227 (2008).
[17]F. Chabri, K. Bouris, T. Jones, D. Barrow, A. Hann, C. Allender, K. Brain, and J. Birchall, Br. J. Dermatol. **150**, 869 (2004).
[18]H. Kalluri, C. Kolli, and A. Banga, AAPS J. **13**, 473 (2011).
[19]J. Matriano, M. Cormier, J. Johnson, W. Young, M. Buttery, K. Nyam, and P. Daddona, Pharm. Res. **19**, 63 (2002).
[20]M. Han, D. K. Kim, S. H. Kang, H.-R. Yoon, B.-Y. Kim, S. S. Lee, K. D. Kim, and H. G. Lee, Sens. Actuators, B **137**, 274 (2009).
[21]H. S. Gill and M. R. Prausnitz, J. Controlled Release **117**, 227 (2007).
[22]See supplementary material at http://dx.doi.org/10.1116/1.4919779 for the video of the drop coating system. This was used to fill the cup regions using drug molecules.
[23]H. Gill and M. Prausnitz, Pharm. Res. **24**, 1369 (2007).
[24]P. Aggarwal and C. R. Johnston, Sens. Actuators, B **102**, 226 (2004).