PUNCTURE DEPTH AND THE MECHANICAL STABILITY OF MICRONEEDLES

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Abstract: Microneedles penetrating less than 1mm beneath the skin can deliver the drugs directly without piercing blood vessels or damaging nerves. The mechanical stability and the puncture behaviour were investigated experimentally by inserting steel needles into silicone rubber and pig skin. Puncture tests revealed that the length of needle buried in the flesh is less than 50% of the nominal insertion depth when the insertion depth is less 1mm. The mechanical stability of the buried needle-flesh assembly, characterized by the force needed to retract the needle, decreased with buried depth and needle diameter. Analysis of the load data suggested that a 100-micron diameter microneedle buried 100 microns deep in pig skin would have a retraction force of 0.1mN, which is only 1% of the retraction force of a conventional needle inserted 5mm into the skin. This suggests that the usage of microneedles in arrays is necessary to increase stability and to enable stable drug delivery.

1 DRUG INJECTION

Drug delivery in hospitals involves modalities as diverse as hypodermal injection, intravenous delivery and oral intake. Drugs taken orally must pass through the digestive system and deal with the first-pass effect of the liver. Numerous drugs, particularly those developed in genetics laboratories, are chemically incompatible with the oral intake route (Orive et al., 2004) They must be directly injected into the body. Hypodermal injection involves training, some pain and potential blood loss, making self-injection at home unwelcome for patients.

Other than direct injection, drugs can be delivered via absorption through the skin. The skin is a natural barrier to foreign chemicals and biological agents. A few drugs such as nicotine and its substitutes have been customized for absorption by the skin. Chemical customization of individual drugs for such absorption is technically challenging, and in many cases, economically unfeasible. Instead of traversing the skin via absorption, solid or hollow microneedles can be used to physically puncture the skin. Drugs can pass through a capillary-scale channel in the hollow needle, or can be delivered as a soluble coating on the needle surface. For such.

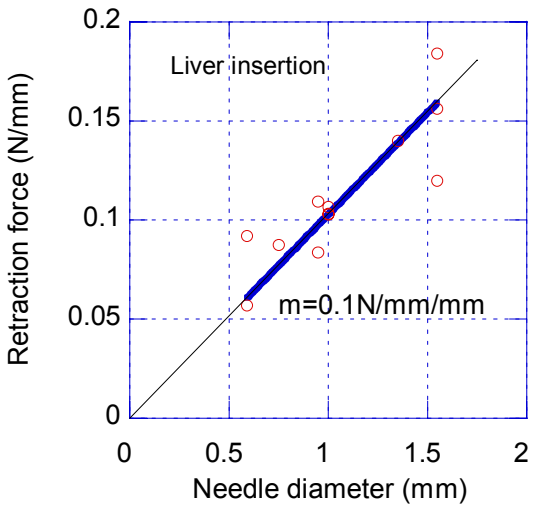

Figure 1: Retraction load for needles with conical and beveled tips. Data from (Okamura).

applications, the microneedles must be long enough to bridge the surface skin layer, but short enough to avoid piercing the blood vessels and nerves that are typically 0.5 – 1mm under the skin surface

There is now a large body of knowledge, processes and tools that have been developed for the design and fabrication of micro- and nanoelectromechanical systems (MEMS and NEMS). A number of researchers have developed silicon microneedles using MEMS processes. (Stoeber & Liepmann, 2005; Staples et al., 2006; Ji, et al., 2006). Silicon microneedle arrays have been fabricated successfully and tested in trials with rats (Nordquist et al., 2007). These tests were concept demonstrations showing that drugs can be delivered using microneedles. However, a variety of issues, including safety concerns about the use of brittle silicon microneedles, remains to be solved. Titanium and polymers are potentially better material choices, and the fabrications of titanium and polymeric microneedles (Parker et al., 2007; Park, Allen & Prausnitz, 2006) has been investigated using MEMS-based processes.

As another alternative to MEMS-based technologies, lasers have been used to create arrays of holes in substrates (Davis et al., 2005). Microneedle pads have been created by plating a metal shell onto the holed surface. The microneedles in arrays fabricated in this fashion are hundreds of microns long, with walls limited to several microns thick because of plating limits. Silicon or metal microneedles fabricated in this way are inherently small because the processes are inherently micron and submicron processes. Recognizing the inherent process limits, microinjection molding suited for fabricating millimeter-scale parts has been used to make polymer microneedles (Sammoura et al., 2007).

Conventional hypodermic needles are typically more than a few millimetres long with diameters typically ranging from 220 microns on up. Such needles are designed to puncture skin and deliver drugs deep underneath the skin. They are not designed for drug delivery at insertion depths of 1mm or less. Limited studies had been conducted to examine systematically the puncture behaviour of such large needles at deep and shallow depths. Long needle puncture studies were conducted by Nguyen & Vu-Khanh on rubber sheets (Nguyen & Vu-Khanh,, 2004) and by Sherwood's group (Sherwood & Fleck, 2004) on solid rubber. They observed significant indentation deformation occurred before puncture in these tests.

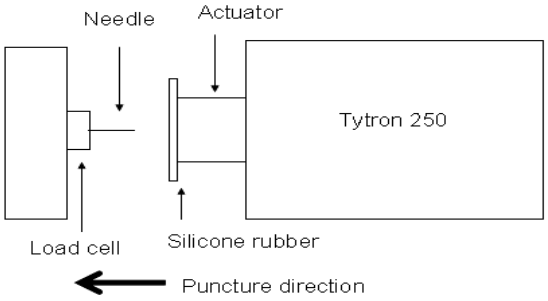

Figure 2: Mechanical testing setup.

For microneedles, where penetration is less than 1mm into the skin, indentation is expected to be significant and to affect drug delivery. The effect of needle diameter had been examined in a study of needle insertion into the liver (Okamura, 2004). The study revealed that the force required to retract the needle was strongly dependent on the needle diameter and the insertion depth (Figure 1). Small microneedles inserted into the surface of the skin should have retraction forces in the mN range and each individual puncture may have low mechanical stability. The effect of depth and needle diameter on the insertion and retraction behaviour were examined this study.

2 INVESTIGATIVE APPROACH

The puncture behaviour of single steel needles pressed to depths of 0.2 to 8mm was examined in this study. Following the methods pioneered by (Sherwood & Fleck, 2004), microstructurally uniform and homogeneous silicone rubber was used

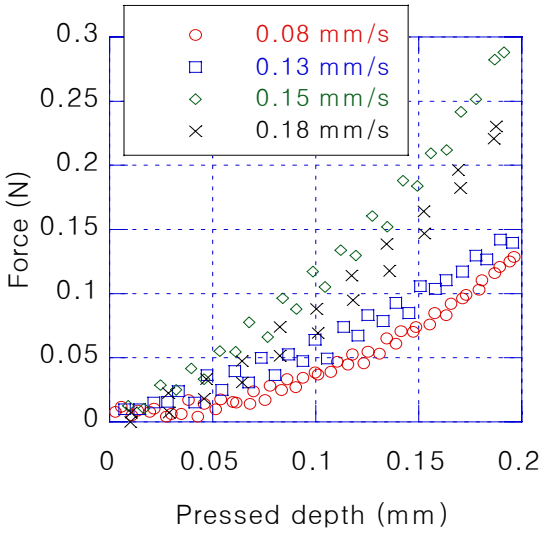

Figure 3: 130-micron needle insertion behaviour in silicone rubber at 0.2mm pressed depth.

as a reference puncture material to examine the puncture behaviour. The puncture behaviour of pig skin was also examined to determine the load and depth range of puncture behaviour in biological materials.

The puncture experiments were conducted on a Tytron 250 press from MTS Systems Corporation equipped with a linear drive actuator. Silicone rubber blocks were cast from a Shin-Etsu silicone premix and cured according to the manufacturer's specifications. Medical grade stainless steel needles 130, 220 or 300 microns in diameter were mounted on a custom designed jig for puncture testing (Figure 2). Once mounted, the loads and positions were calibrated. The needle was held fixed while the silicone rubber casting was moved toward the needle

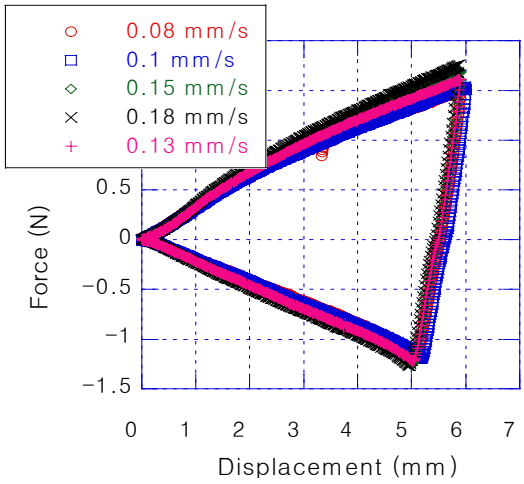

Figure 4: 130-micron needle insertion behaviour in silicone rubber at 6mm maximum pressed depth.

at displacement rates of 0.1 mm/s, 0.13 mm/s, 0.15 mm/s or 0.18 mm/s to a target maximum pressed depth (MPD), and then reversed at the same rate. The experiment ended when the displacement reached zero. The experiment was repeated for a range of MPDs from 0.2 mm to 8 mm.

3 RESULTS AND ANALYSES

3.1 Shallow Insertion Depths

The load-displacement results at 0.2mm MPD are shown in Figure 3. The curves indicate that the peak load was displacement rate dependent. At each displacement rate, the unload curve collapsed onto the load curve. This indicates that the deformation recovered elastically without puncture. The absence of a hysteresis between the load and unload curves indicates that no energy was dissipated at 0.2mm MPD. In addition, the higher peak loads at higher

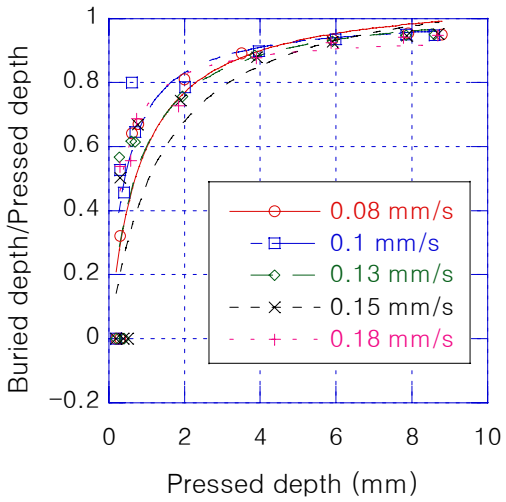

Figure 5: Ratio of buried to pressed depth for needle insertion into silicone rubber using 130-micron needles.

displacement rates did not result in puncture. This suggests that needles less than 0.2mm long have difficulty in puncturing soft silicone rubber.

3.2 Puncture Depth

The results at 6mm MPD are plotted in Figure 4. As with the tests in Figure 3, the displacement was reversed from loading to unloading in each trial upon reaching the 6mm maximum set displacement. The unloading curves did not retrace the loading

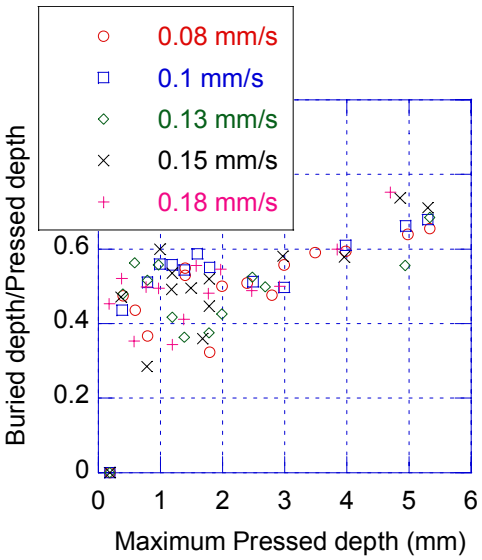

Figure 6: Ratio of buried to pressed depth for needle insertion in pig skin using 130-micron needles.

curves, but rather intersected the zero load line to the right of the triangle, crossing into the tension region. Unlike the penetration behaviour at 0.2mm MPD, where the needle was fully withdrawn at zero load, the needle retracting from 6mm MPD remained buried in the rubber. This zero load depth on retraction was taken to represent the buried depth on insertion. A plot of the buried needle depth normalized by the MPD is plotted in Figure 5. At large MPDs, the ratio approached unity, but at MPDs less than 1mm, the ratio was significantly less than one. The low ratios at settings below 1mm indicate that an increasingly significant proportion of the needle was left outside the solid during the loading phase.

The MPD for needle insertion into pig skin is plotted in Figure 6. Biological materials are less uniform and the ratio is more scattered. Despite this, the trend is similar to that observed with the silicone rubber in that the ratio approaches unity at large pressed depth, but is 0.5 or less when the pressed depth was 2mm or less.

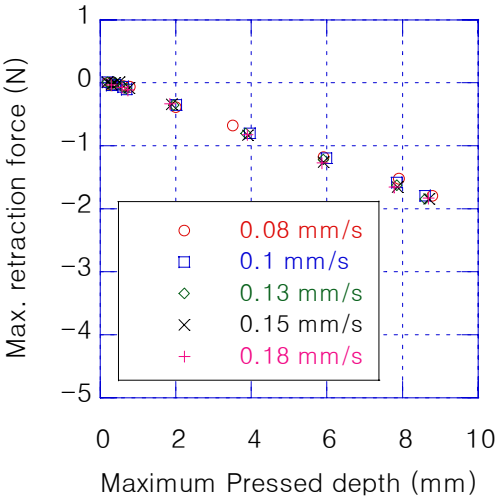

Figure 7: Maximum retraction force for 130-micron needle insertion into silicone rubber.

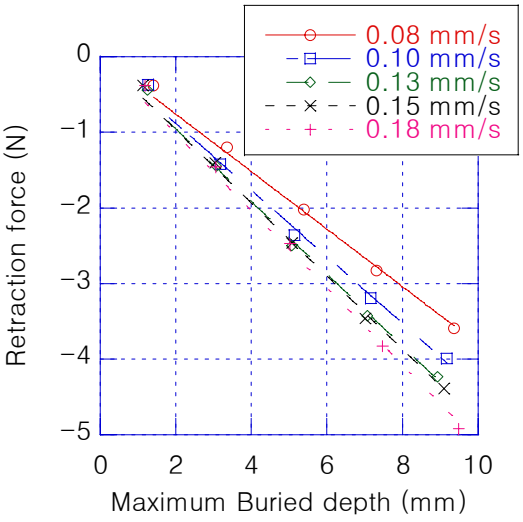

Figure 8: Maximum retraction force for a 300-micron needle inserted into silicone rubber.

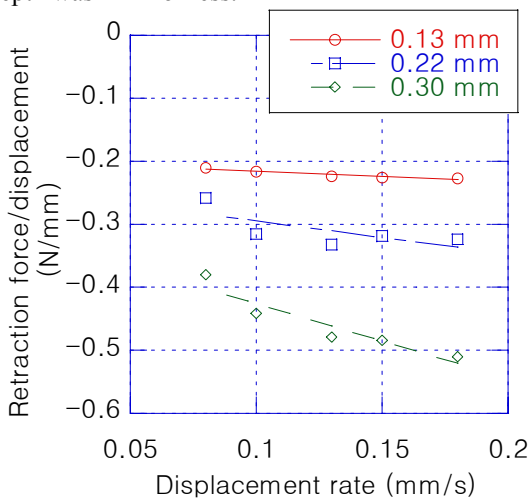

Figure 9: Rate dependence of retraction force per unit of buried needle length for needle insertion into silicone rubber.

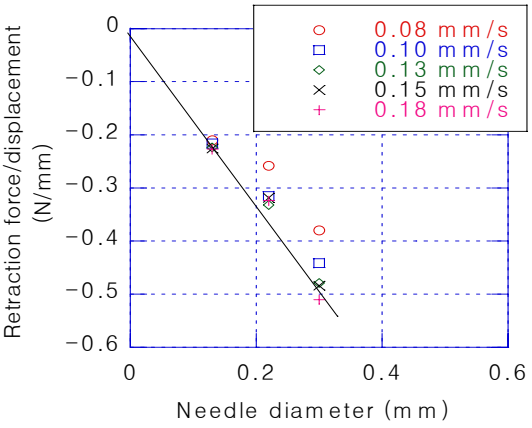

Figure 10: Diameter dependence of retraction force per unit of buried depth in silicone rubber.

3.3 Retraction Force

The maximum retraction load (MRL; bottom right apex in Figure 3) required to pull a 130-micron needle out after pressing is shown in Figure 7. The data show that the retraction forces at different displacement rates collapsed onto a single line for the 130 micron-needle. The MRL for the 300-micron needle is plotted in Figure 8. The MRL for this larger needle was clearly displacement

dependent. The MRL was markedly higher at higher retraction rates. Thus, while the 130-micron needle's rate dependence appeared negligible, this was not the case with larger diameter needles. The rate of change of the MRL with buried depth as a function of the displacement rate is plotted in Figure 9. The plot shows that the rate dependence was linear for all the needles tested, and that the MRL decreased with decreasing needle diameter. The influence of needle diameter is plotted in Figure 10. The MRL was greatest at high displacement rates. Fitting a straight line through the data with the highest displacement gives a slope of -1.6N/mm/mm, which is the MRL per unit of buried depth and needle diameter. Using this as a basis for estimate, in Figure 11 a line is plotted and compared with the retraction loads observed with a 130-micron needle at depths less than 1000 microns. The comparison showed reasonable agreement between the data and the prediction.

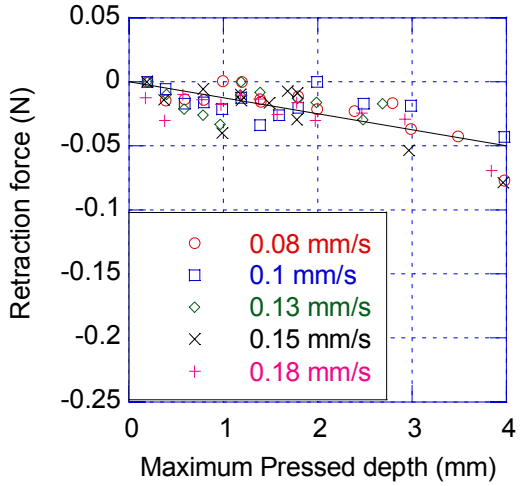

Figure 11: Comparison of maximum retraction force with model (line) at shallow pressed depth.

The MRL for insertion into pig skin is plotted in Figure 12. As expected, the magnitude of the MRL increased with the actual buried depth, but the displacement rate dependence cannot be delineated given the greater scatter. The rate of change of the MRL per unit of buried depth and needle diameter was approximately 0.1N/mm/mm.

4 DISCUSSION

The length of the needle buried in the flesh during hypodermal insertion is generally assumed to equal to the pressed depth. This assumption is reasonable for deep insertions, but breaks down when the needle is less than 2000 microns long. At pressed depths under 1000 microns, less than half of the needle maybe buried; and no penetration was observed at pressed depths less than 200 microns. Since the lengths of microneedles fabricated using MEMS processes are limited by the thickness of the wafer, which is typically less than 300 microns thick. Silicon microneedles less than 300 microns long may have difficulty in puncturing the skin. If punctured, the maximum buried depth will likely be less than 100 microns.

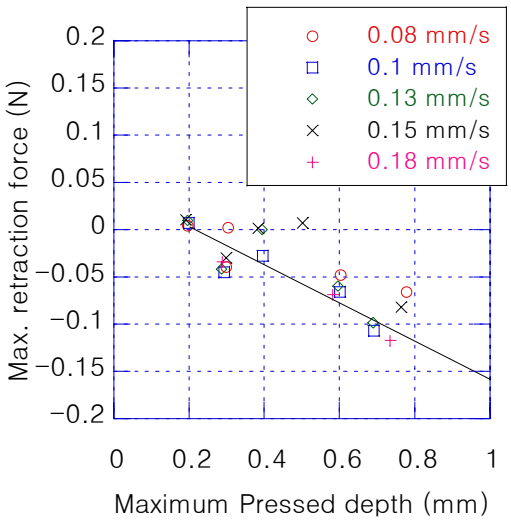

Figure 12: Retraction force for 130-micron insertion in pig skin.

Another issue is the mechanical stability of the microneedles. When punctured, the surrounding material in the puncture will exert traction onto the buried needle and prevents it from slipping out of the puncture hole. The retraction force was found to decrease at a rate of -1.6N/mm of buried depth/mm of needle diameter for silicone rubber, and -0.1N/mm/mm for pig skin (Figure 12). In comparison, the corresponding value for the case of needle puncture into liver is -0.1N/mm/mm. Using this as an estimate for biological materials, a 0.1mm microneedle buried 0.1mm into the skin would have a retraction force of 1mN. A conventional 0.22mm needle inserted into flesh 5mm would have a retraction force of 110mN, which is 100 times greater. If an array of 110 microneedles were used, the retraction force can be increased to 100mN such that the microneedles can remain stably buried to allow stable drug delivery. The puncture behavior and the design guidelines for stably drug delivery are reported in another paper.

5 CONCLUSIONS

Examination of the puncture behaviour needles with a silicone rubber model indicated that indentation effects are significant at shallow insertion depths for both silicone rubber and pig skin. Less than 50% of the needle may be buried because of indentation when short microneedles are used. The investigation also revealed that the retraction force providing mechanical stability to the needle in the skin was linearly proportional to the buried depth and the needle diameter. Short microneedles with small diameters will have low retraction forces and poor mechanical resistance against being dislodged.

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