Medical Engineering and Physics 000 (2017) 1–9

Contents lists available at ScienceDirect

Medical Engineering and Physics

journal homepage: www.elsevier.com/locate/medengphy

# Experimental and modelling characterisation of adjustable hollow Micro-needle delivery systems

Ting-Ting Liu, Kai Chen*, Min Pan

*School of Mechanical Engineering, Hangzhou Dianzi University, Hangzhou, Zhejiang 310018, China*

ARTICLE INFO

*Article history:*
Received 22 January 2017
Revised 28 July 2017
Accepted 21 August 2017
Available online xxx

*Keywords:*
Hollow micro-needle
Resistance pressure
Drug delivery

ABSTRACT

*Background:* Hollow micro-needles have been used increasingly less in practice because the infusion into the skin is limited by the tissue resistance to flow. The relationship between the infusion flow rate and tissue resistance pressure is not clear.

*Methods:* A custom-made, hollow micro-needle system was used in this study. The driving force and infusion flow rate were measured using a force transducer attached to an infusion pump. Evans blue dye was injected into the air, polyacrylamide gel and in-vivo mouse skin at different flow rates. Two different micro-needle lengths were used for in-vivo infusion into the mouse. A model was derived to calculate the driving force of the micro-needle infusion into the air, and the results were compared to experimental data.

*Results:* The calculated driving forces match the experimental results with different infusion flow rates. The pressure loss throughout the micro-needle delivery system was found to be two orders smaller than the resistance pressure inside the gel and mouse skin, and the resistance pressure increased with increasing flow rate. A portion of liquid backflow was observed when the flow rate was relatively larger, and the backflow was associated with a sudden larger increase in resistance pressure at a higher flow rate.

*Conclusions:* The current micro-needle delivery system is capable of administering liquid into the mouse skin at a flow rate of up to 0.15 ml/min, without causing significant backflow on the surface. The resistance pressure increases with increasing flow rate, causing infusion restriction at higher flow rates.



## 1. Background

Patch-based drug delivery offers certain appealing features, such as non-invasiveness and the ability to provide controlled release over time. However, it faces a significant challenge in increasing skin permeability, as most macromolecular drugs exhibit poor permeability owing to the existence of stratum corneum as a natural barrier [1,2]. Other approaches have been applied, such as chemical/lipid enhancers and physical means of assisting permeability to overcome the skin barrier. However, these methods are rarely used in clinical applications for various reasons, such as skin allergies, low effectiveness and inconvenience [1,2]. Traditional hypodermic needles have dominated subcutaneous injections, but are often associated with problems such as pain, trauma, bleeding and lack of precise control of injection rate and dosage.

The micro-needle array, which originates from microelectronic manufacturing technology, has emerged as a promising technology that combines the non-invasive features of drug patches with the effectiveness of hypodermic needle injection [2-5]. A micro-needle array typically refers to dozens or hundreds or more of needle-like projections of less than hundreds of microns in length. The micro-needles can be divided into two categories: hollow and solid. Hollow micro-needles are often combined with a micro-pump or syringe to create a controlled drug delivery system [6,7]. However, hollow micro-needles offer very limited flow rates, apparently because of the low flow conductivity in the skin, as well as the compression of dense dermal tissue that causes flow resistance [8-12]. Solid micro-needles are reported to enhance permeability by creating micro channels in the stratum corneum, or to directly induce coated drugs during their insertion into the skin [13,14]. Recent research trends have mainly focused on the design and manufacture of dissolvable or biodegradable solid micro-needles. Drug-coated or encapsulated micro-needles can be dissolved into bodily fluid after being pierced into the skin [15,16,17,18]. The micro-needle array can also be integrated with other techniques, such as optical trapping, to trap, store and deliver drug molecules/cells in specific targets [19].

*Abbreviations:* eb, evans blue; Di, deionization; Km, kunming; Asp, ammonium persulfate; Temed, n,n,n',n'-tetramethylethylenediamine; SDS-PAGE, Sodium dodecyl sulfate polyacrylamide gel electrophoresis; GLP, Good laboratory practice.

* Corresponding author.
*E-mail addresses:* liutingting817@163.com (T.-T. Liu), kchen@hdu.edu.cn (K. Chen), 1963622327@qq.com (M. Pan).

http://dx.doi.org/10.1016/j.medengphy.2017.08.012
1350-4533/

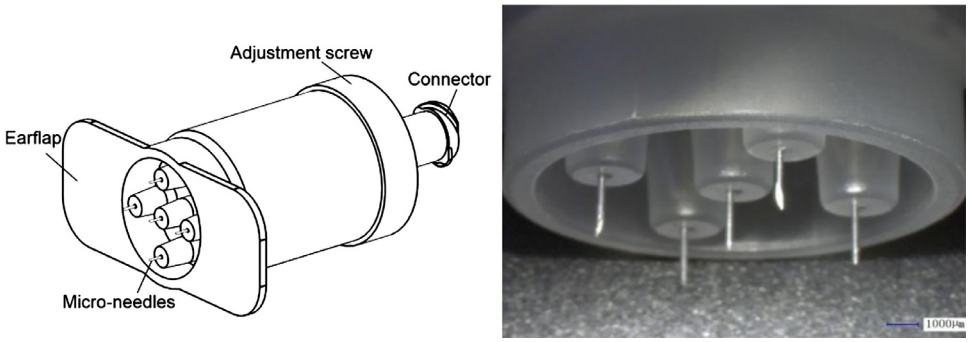


**Fig. 1.** Structural illustration of self-made micro-needle system.

Ideally, hollow micro-needles should offer more extensive clinical applications than solid micro-needles in terms of their feature of continuous and controlled drug release. However, these needles have generally received less attention and have been less frequently used, owing to the practical problem of restricted flow caused by compressed dense dermal tissue. The drug diffusion through the skin is also related to the length of the needle inserted into the skin, and the diffusion rate will be significantly reduced if the lengths are too small [20]. Furthermore, the micro-needles should not be so long as to touch the nerves, thus causing pain. The majority of studies on hollow micro-needles involved in vitro experimental performance. At present, Soluvia® and MicronJet® are the only hollow micro-needle systems available commercially for therapeutic applications [21]. However, the one micro-needle in Soluvia® and three micro-needles in MicronJet® are larger in size and longer in length than the common micro-needles fabricated from etching processes.

In the current study, a stainless-steel hollow micro-needle system was designed and fabricated. The size of the current micro-needles was also deliberately made larger than the micro-needle arrays made from microelectronic etching processes, to overcome tissue resistance and reveal the flow characteristics of the infusion process. The liquid was injected into air, polyacrylamide gel, and then mouse skin, through a syringe-driven micro-needle system. The driving force of the syringe (or infusion force) was recorded using a transducer. A physical model for calculating the driving force for infusions in the air was proposed and verified through experiments. By comparing the infusion force for both the gel and subcutaneous infusions, with reference infusions in the air, the resistance pressure can be obtained.

## 2. Methods

### 2.1. Fabrication of micro-needle system

The micro-needles were fabricated using the traditional injection moulding process. They were prepared by fine grinding of tiny stainless-steel tubes and embedded into the needle base by a fluid dispensing process. A structural illustration of our self-made micro-needle system is provided in Fig. 1. It includes five separated micro-needles, with one located in the centre and the other four circularly distributed at a radial distance of 3 mm. There are two earflaps for attachment to the skin, a screw to adjust the micro-needle projection length, and an end connector for connection to a syringe or an infusion pump. The outer and inner diameters of the micro-needle are 260 $\mu$m and 180 $\mu$m, respectively. The extended length of the micro-needle can be adjusted from 0 to 2.80 mm. Although the needle size of the self-made array is much larger than the micro-needles fabricated by the microelectronic etching process, it is still very small compared to commonly used hypodermic needles; therefore, it is still referred to as a micro-needle. Fig. 2 shows a single needle with two different lengths (1 mm and 2 mm).

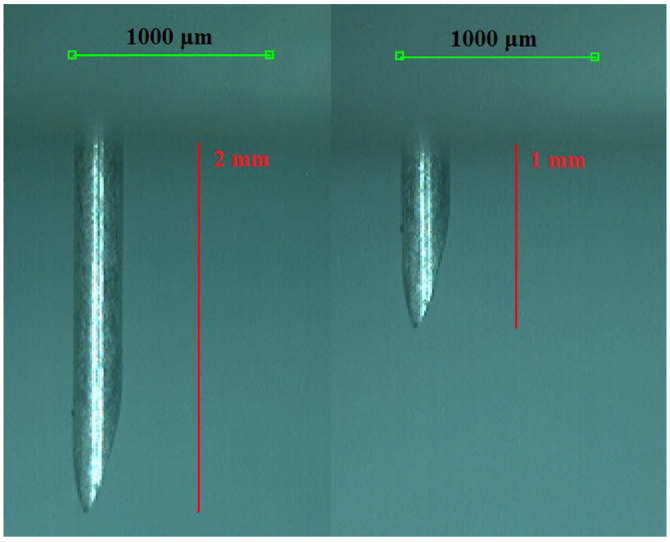


**Fig. 2.** Photo of single micro-needle with two different adjusted lengths.

### 2.2. Ex-vivo experiments

Hollow micro-needle infusions are usually performed using a pen-like syringe or precision infusion pump. The force delivered by infusion devices, either infusion pumps or syringe devices, must overcome both the resistance in the infusion system and that in the body tissue, to enable the liquid drug to flow into the skin. In the current study, a precision syringe pump was selected for the experiments. The experimental setup is shown in Fig. 3. The pump (Pump 11 Elite, by Harvard Apparatus, MA, USA) has a microprocessor controller to stabilize the pre-set flow rate, which can range from 1.28 pl/min to 88.28 ml/min, with a reappearance difference of less than 5%. A 2.5 ml standard syringe with an inner diameter of 8.4 mm was selected and connected to the micro-needle system through a soft silicon rubber tube, with a length of 100 mm and inner diameter of 1.4 mm. The syringe was clamped in a V-shaped guide groove of the precision pump, driven by a step motor. A force transducer (5) with a frequency response of 1 ms (FSG-15N1A, Honeywell, USA) was fixed to the push block of the precision pump platform (4), and the output end of the sensor was connected to a differential amplifier (1) (INA101 BB, TI, USA), in which the signal is amplified, transferred to a data collector (2) (USB7660, Zhongtai YanChuang, China), and then to a computer (3). The sampling rate for the data collection system is 1 kHz. Because the advancing

Please cite this article as: T.-T. Liu et al., Experimental and modelling characterisation of adjustable hollow Micro-needle delivery systems, Medical Engineering and Physics (2017), http://dx.doi.org/10.1016/j.medengphy.2017.08.012