Application Note

# Non-contact microneedle coating utilizing drop-on-demand PipeJet® technology: advanced by automated droplet volume calibration and needle detection

## Introduction

Microneedle (MN) patches are the innovative and minimaly invasive transdermal drug delivery system of the future. These patches consist of multiple tiny needles measuring around 0.5 mm in height arrayed with a pitch smaller than 1 mm [1]. In contrast to common hypodermic needle-based drug deliveries, these patches are applied to penetrate the outermost skin layer (stratum corneum) and only deliver large biomolecules, such as drugs or vaccines into the viable epidermis [2]. Further, MN patches have the advantages of being small, have individual packaging, do not require cold chain storage, and are painless to self administer [3]. While these consumer and patient features are attractive, by adherence of biomolecules onto micron-scale sharp protrusions is very challenging for manufacturers. The small size of MNs enforces the deposition of uniform and reproducible drug load onto the upper half of the MN shaft, where the percutaneous absorption takes place after the needle insertion [2].

A successful implementation of the requirements of drug loading is realized applying the PipeJet® technology. It exploits the great stability of piezo actuation, enabling the precise delivery of identical droplets at any desired low volume from 2 to 70 nl per droplet. Further, the PipeJet® Nanodispenser offers a robust dispensing of coating formulations containing viscous excipients or various surfactants and efficiently maximizes the drug load on a MN tip, by depositing a viscous nanoliter droplet instead of adding up multiple picoliter droplets. The contribution of the precise drop-on-demand deposition and low dead volume can efficiently diminish waste of material.

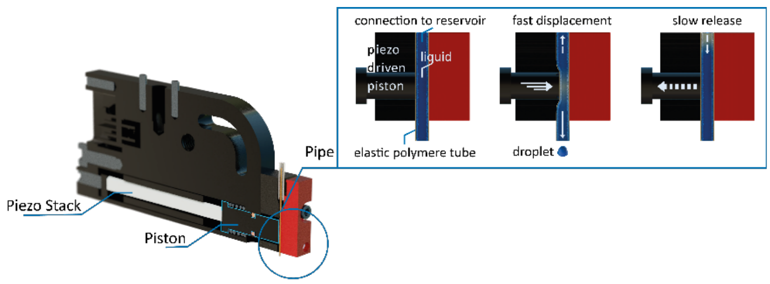


Figure 1: The PipeJet® working principle with an elastic polymer tube and piezoelectric actuation enforces a direct volume displacement for a non-contact droplet delivery.

The PipeJet® technology, with its piezo actuated mechanism, optimizes the impact of an in-coming droplet hitting a MN tip by precisely controlling its speed. This level of control secures droplet integrity, lowers the risk of substrate contamination, and minimizes the number of broken droplets. By using a BioFluidix liquid handling platform, the BioSpot® workstation (see Fig. 1), an automated coating process of a MN patch can be implemented.


**Figure 1: The BioSpot® Workstation combines a high precision staging with nanoliter dispensing for a precise and reliable droplet deposition onto MN tips.**

The BioSpot® workstation is equipped with several process control features to assist the workflow, e.g. optical systems, such as the SmartDrop System and the TopView Camera. The SmartDrop System implements fully automated volume calibration of ejected droplets independent of the liquid classes. This technology guarantees an appropriate loading of MNs with the intended amount of coating formulation. The Microneedle add-on for the BioSpot® Control Software works closely with a substrate directed camera (TopView Camera) for vision based detection of the individual MN tips. The image data is translated into three-dimensional coordinates to set the targets for droplet deposition. In combination with the implemented flight path correction (dispenser alignment tool) an optimal spotting accuracy is achieved. A final quality control process ensures the correct droplet deposition as well as the integrity of droplets. Thus, the operator can efficiently set up a reliable, reproducible and automated microneedle coating process, with individual dispensing patterns for each individual MN patch to compensate for fabrication tolerances of the substrate or loading failures by the operator.

**Automated microneedle working process**

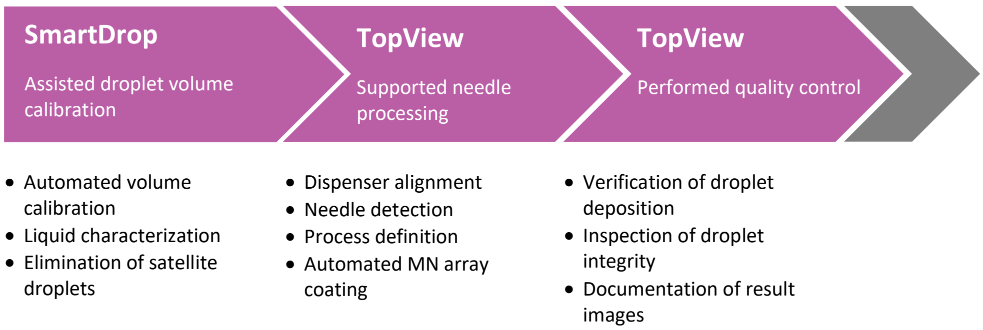


**Figure 2: Schematic illustration of the automated microneedle coating process from volume assignment, needle spotting to quality control.**

## Materials and methods

To guarantee a successful coating of the upper half of each individual MN tip, cf. fig. 2, the liquid properties of the applied liquids are determined and if necessary, modified by adding proven viscosity enhancers or surfactants. The SmartDrop System automatically adjusts the dispensing parameters to deliver droplets at the desired target volume. A stability study led to an optimized and recommended composition of the coating solution consisting of 50% glycerol and 15% trehalose. After initial set up, the dispenser alignment was accomplished to compensate for flight path aberrations.

The introduction of a novel needle detection algorithm allows for the automated identification of all individual needle tips without any user interaction. The automatically defined spotting pattern is executed by applying the SmartDrop defined dispensing parameters in the on-the-fly mode, which means the droplets are ejected when the staging is in motion allowing a fast processing of the MN patch. Finally, the TopView Camera is applied for quality verification.

## Results

Long term dispensing stability tests using typical coating media demonstrated that the PipeJet® technology has great competence in dispensing various liquid samples at different viscosities and surface tensions. The performance of all tested aqueous solutions of coating excipient has revealed $CV_{1000*}$ less than 2 %. Specifically, the optimized coating formulation at 50% glycerol and 15% trehalose revealed a $CV_{1000}$ less than 1%.

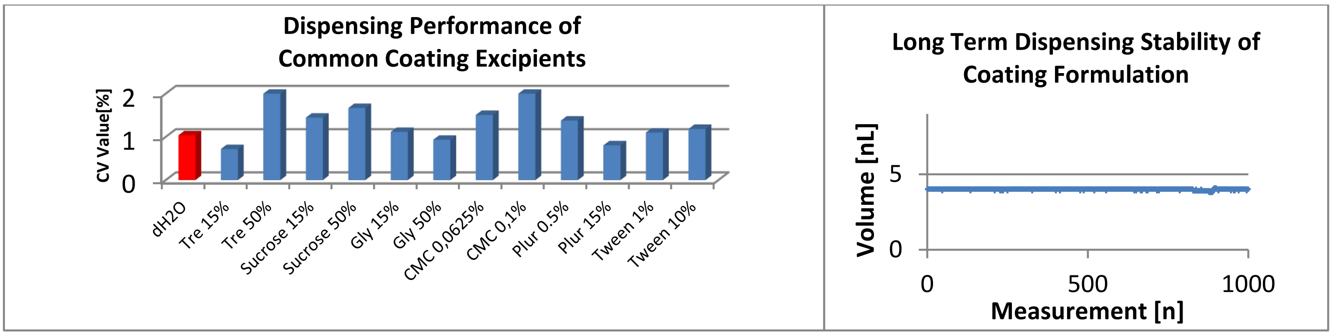


**Figure 3: The bar graph (left ) illustes the dispensing performance of the common coating excipients in aqueous solution. The line graph (right) shows the long term stability result of 1000 measurements of the coating formulation.**

Numerous MN patches were coated applying the optimized solution in combination with the described process at a target volume of 4 nL per droplet. The success $rate_{400**}$ was determined to be at 97%, thus 97% of all processed individual needle tips were covered by a 4 nl droplet on their upper half.

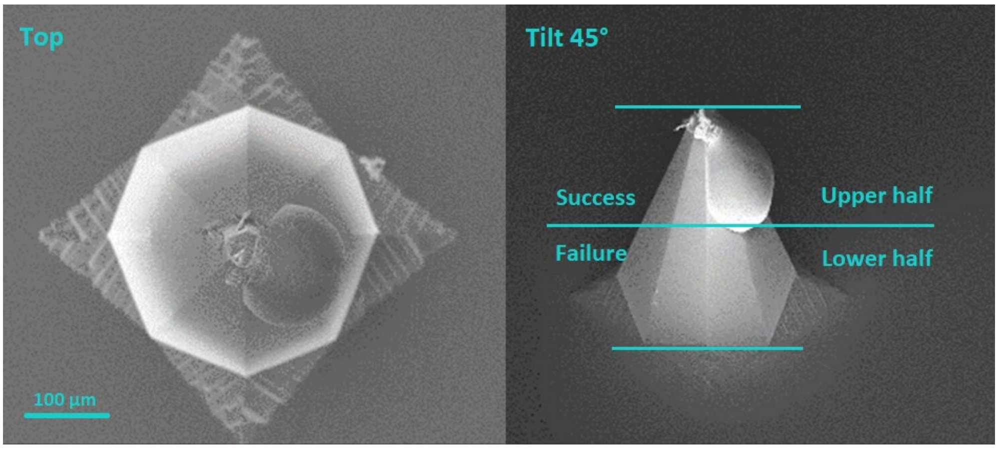


**Figure 4: The images show a coated MN with a 4 nL coating formulation droplet perching on the tip under scanning electron microscopy (SEM) from two different angles.**

## Summary

The BioSpot® assisted microneedle coating process is designed to be suitable for each and every individual type of microneedle array, where individual spotting patterns and required droplet volumes can be customized. The PipeJet® technology enables robust dispensing of various coating formulations in the nanoliter range. Both, droplet deposition and single droplet volume are optimized for the highest accuracy and precision. BioFluidix modifies the coating solution to achieve maximum dispensing stability, and implments the automated process to make spotting MNs reliable , effortless and fast.

## Reference

[1] „Tyndall National Institute," [Online]. Available: https://www.tyndall.ie/transdermal-drug-delivery. [08/03/2020].

[2] R. F. Donnelly, T. R. R. Singh, E. Larrañeta und M. T. McCrudden, „Microneedles for Drug and Vaccine," JohnWiley & Sons Ltd, 2018.

[3] S. J. Draper, J. B. Carey, C. O'Mahnoy, A. Vrdoljak, M. G. McGrath, A. V. Hill, A. M. Crean und A. C. Moore, „Coated Microneedle Arrays for Transcutaneous Delivery of Live Virus Vaccines," J Control Release.

* 1000 individual volume measurements of the solution
** The success rate is determined from a  total of 400  coated MN samples.