PipeJet® Nanodispenser Technology

WHITE PAPER

BioFluidix GmbH

August 2023

Introduction

Dispensing liquid volumes in aliquots of a few nanoliters at high reliability, reproducibility and accuracy gets increasingly important in production processes of pharmaceutical and diagnostic products. Examples include modern diagnostic point of care tests (POC) [1] and innovative drug delivery formats like microneedle patches (MNP) [2] or oral thin films (OTF) [3].

In comparison to conventional pipetting systems, non-contact dosage systems deliver liquid aliquots as free-flying droplets. These systems are advantageous over conventional ones, since the droplets can be deposited with a high spatial resolution on arbitrary surfaces. This enables a homogeneous distribution of liquids on substrates.

Due to the wide range of liquid types used in the mentioned applications the dispensing system is challenged with various rheological and liquid properties. It must be robust to viscosity and viscosity changes, surface tension and density from liquid to liquid. The increasing demand on handling cell solutions or particle loaded suspensions (e.g. magnetic beads) adds further requirements on a versatile and robust dispensing system.

Furthermore, pharmaceutical and diagnostics production processes must be compliant to Good Manufacturing Practice (GMP). Therefore, the dispensing system must employ interchangeable fluidic components to exclude any cross-contamination.

The BioFluidix' PipeJet® technology satisfies all these requirements, implementing the most versatile solution in a simple and very robust nanoliter dispensing system.

PipeJet and Components

Figure 1 provides a quick overview of the PipeJet® components. Centerpiece of the PipeJet®-technology is the dispensing pipe, a low-cost elastic polymer pipe. It is a two-component assembly consisting of a cylindrically shaped nozzle pipe and a connector. A typical nozzle pipe is made of polyimide, whereas the connector is made of polypropylene (PP) or polyether ketone (PEEK). The dispensing pipe is clamped between two pipe guides and mounted to the dispensing module. This allows for an effortless exchange of dispensing pipes on demand. The PipeJet®- nanoDispenser can be directly installed into production lines or used with BioFluidix' BioSpot® lab-automation workstation.

Liquid supply to the dispensing pipe is realized by the 1/16" connector at the back end of the pipe connected to a reservoir holding the sample to be dispensed. Depending on the individual requirements, different reservoirs can be employed, including tubes or pipette tips for small volumes or the BioFluidix SmartReservoir, which provides controlled reservoir conditions for critical production processes. The PipeJet®-technology does not require external pressurization, since the small pipe diameters allow for passive capillary priming of the system.

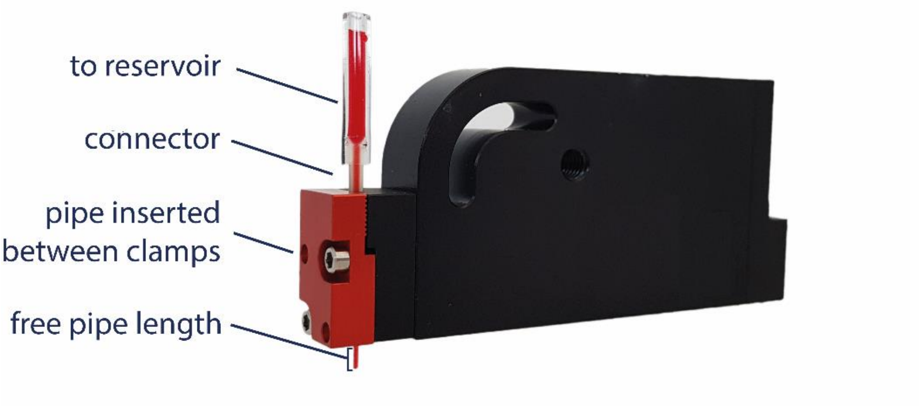

Figure 1: PipeJet® nanoDispenser: The disposable pipe is inserted between to pipe guide clamps. A connector at the top of the pipe enables the connection to the reservoir by an 1/16" tubing. The free pipe length is the length of the pipe that protrudes out of the clamps.

The dispensing pipes are available at different diameters, which enable the ejection of droplets in specific volume ranges. Hydrophobic surface treated versions are available for specific liquid types. Standard sizes are available with inner diameters (ID) of 500 µm, 200 µm and 125 µm. The available standard sizes, the addressable volume ranges as well as the corresponding working volumes are summarized in table 1.

The "free pipe length" describes the length of the pipe which protrudes out of the PipeJet module. Available free lengths range from 11 mm (xl), 9 mm (l) to 3 mm (s). Pipes with a longer free length are ideal for applications, which require positioning of the orifice close to surfaces which are difficult to approach. The systems working volume or dead volume is the minimum pipe volume that must be filled to ensure a reliable performance and is dependent on the geometry of the individual pipe types.

Table 1: Available standard sizes of dispensing pipes with corresponding dispensing and working volumes.

Pipe type (=inner diameter)	Index (free pipe length)	Volume	Dead volume
125	S (3 mm)	2 – 8 nL*	0,4 µl
200	S (3 mm)	8 – 20 nL*	0,7 µl
	L (9 mm)	8 – 20 nL*	0,9 µl
500	S (3 mm)	20 – 70 nL*	4,5 µl
	L (9 mm)	20 – 70 nL*	5,5 µl
	XL (11 m)	20 – 70 nL*	6,5 µl

* Volume ranges refer to dispensing DI-water at RT.

Droplet Generation with the PipeJet

The patented PipeJet® technology enables non-contact dispensing of droplets at volumes from 2 to 70* (*pure water) nanoliters per droplet.

The robust dispensing mechanism applies the aforementioned polymer pipe acting as outlet nozzle. A controlled deformation of the elastic pipe implies a fast volume displacement, which is forcing the sample out of the nozzle as a single droplet. The deformation of the elastic pipe, mounted in the pipe guides, is achieved via a piston driven by a high-quality piezo stack actuator.

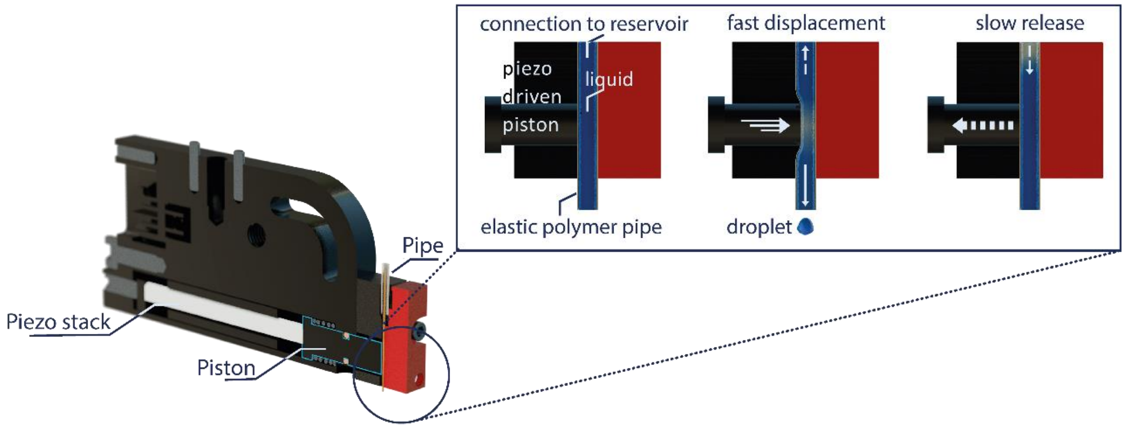

Figure 2: Working principle of the PipeJet® nanoDispenser: A droplet is ejected as result of fast deformation of the polymer pipe by the piezo driven piston.

The droplet volume is defined by the amount of deformation whereas the droplet quality is adjusted by the speed of the deformation.

Due to the surface energy of the liquid at the pipe nozzle, droplets in the nanoliter range do not passively detach from the liquid column. Therefore, the kinetic energy introduced by the piston must overcome this surface energy. A too low energy input does prevent a droplet tear of, whereas too high energy input leads to the generation of several droplets, so called “satellite droplets”. The kinetic energy is directly related to the mentioned speed of deformation (piezo stroke velocity)

A higher piezo stack extension results in a large deformation of the pipe and therefore an increasing droplet volume. The correlation between piezo extension length and droplet volume is closely related to the used liquid type and dispensing pipe. By way of example this correlation is presented in Figure 3 for a 125 µm pipe with water.

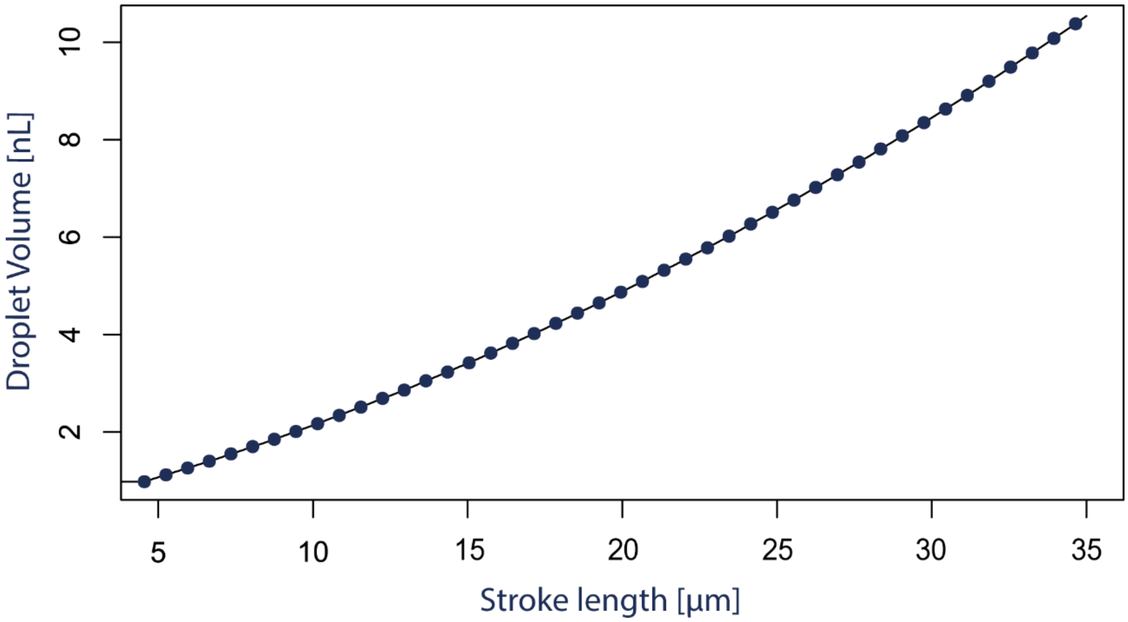

Figure 3: Relation between piezo stroke length and droplet volume for water in the 125 µm pipe.

Both parameters, the piezo stack extension as well as the stroke velocity, can be controlled using the BioFluidix CX 200 controller. The Graphical User Interface of the BFX client software allows a convenient tuning of these parameters for an ideal dispensing process. BioFluidix' SmartDrop technology offers an automatic droplet volume calculation and calibration, using an optical image analysis.

The dispensing process is finished by the slow release of the piston, which resets the deformation of the pipe. The dispensing pipe is refilled by capillary forces, which are defined by the pipe geometry and the liquid properties. This capillary refill process is limiting the maximum applicable flow rate depending on pipe diameter and liquid viscosity. For instance, with pipe ID 500 and pure water a maximal flow rate of 2500 nL/s can be achieved, which reduces with the smallest pipe (ID 125) to 200 nL/s. If higher flow rates are required, it can be increased by the application of the BioFluidix SmartReservoir.

Dispensing a wide range of liquid types

The PipeJet® technology is applicable to a wide range of liquid types. Examples include buffers, solvents, living cell suspensions or detergents. Due to the polymers used, the dispensing pipe is highly resistant against bases and acids. Furthermore, it is compatible with organic solvents like DMSO, acetonitrile, methanol, ethanol, etc.

Viscosities up to 150 mPas can be dispensed in a precise and robust manner. Each specific liquid type requires a specific set of dispensing parameters to produce reproducible and high-quality droplets. As described above the kinetic energy must be adjusted to achieve optimal droplet tear off. For aqueous solutions piezo stroke velocities of 60 – 80 µm/ms are recommend. For liquids with a lower surface tension less kinetic energy is necessary with piezo stroke velocities of 40 – 60 µm/ms. For viscous liquids the kinetic energy must be increased to stroke velocities from 100 - 400 µm/ms.

Conclusion

In conclusion, the PipeJet® technology is a simple and robust nanoliter dispensing system and enables non-contact dispensing of highly reproducible droplets at very low volumes. The used material of the dispensing pipe allows together with the robustness of the technology the dispensing of a wide range of liquid types from organic solvents to viscous liquids and suspensions.

Major advantage is the low-cost dispensing pipe, allowing for low operating cost and making the PipeJet® technology especially suitable for disposable applications in critical environments (e.g. GMP).

The PipeJet® technology can be integrated into production lines, is available as OEM component or is integrated in BioFluidix' BioSpot®, a lab-automation and liquid handling workstation.

References

[1] Quesada-Gonzalez, D., Stefani, C., Gonzalez, I., De La Escosura-Muñiz, A., Domingo, N., Mutje, P., & Merkoçi, A. (2019). Signal enhancement on gold nanoparticle-based lateral flow tests using cellulose nanofibers. *Biosensors and Bioelectronics*, *141*, 111407.

[2] Lee, J., van der Maaden, K., Gooris, G., O'Mahony, C., Jiskoot, W., & Bouwstra, J. (2021). Engineering of an automated nano-droplet dispensing system for fabrication of antigen-loaded dissolving microneedle arrays. *International Journal of Pharmaceutics*, *600*, 120473.

[3] Siddiqui, M. N., Garg, G., & Sharma, P. K. (2011). A short review on “A novel approach in oral fast dissolving drug delivery system and their patents”. *Adv Biol Res*, *5*(6), 291-303.