PRESSURE DRIVEN AND REGULATED DISPENSER FOR THE MICROLITER RANGE

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ABSTRACT

We report a sensor controlled normally closed non-contact fluid dispenser for the microliter range. A commercial disposable syringe is filled with fluid and connected through a T-connector to a pressure sensor separated from the liquid by an enclosed and defined gas volume. The other end of the T-connector is connected to a conventional dispensing valve which is normally closed. By displacement of the syringe plunger a defined pressure inside the enclosed gas volume can be established, controlled by the pressure sensor. The valve is then opened to release a pressure driven liquid jet. It is closed again when a certain pressure difference is detected by the sensor. Dispensed volumes can be easily changed by tuning this pressure difference. Experiments have been performed with water for volumes between 500nl and 25µl with standard deviations below 5%.

KEYWORDS

syringe-solenoid dispenser, pressure driven dispenser, liquid jet, micro dispensing

INTRODUCTION

The precise non-contact dispensing of volumes between 500nl and 25µl is an important issue for in-vitro-diagnostics (IVD), high-throughput screening (HTS) and industrial applications [1, 2]. Covering such a large range with high precision is a challenging problem, especially when non-contact dispensing of different liquids is required. Currently mainly pipetting tools are used for this purpose, which suffer from following shortcomings: First they are in mechanical contact with the substrates and/or aspirating fluids, thus introducing a high risk of cross-contamination that can be only avoided by intensive and time consuming cleaning protocols. Second there is no indicator or sensors providing a positive confirmation that the quantity of the dispensed liquid matches the requested volume. The development of a normally closed non-contact dispenser for handling a large variety of liquids, capable to determine in real-time (i.e. "online") the volume of the dispensed liquid is thus of high interest for many applications, not only within IVD. In this article we present a normally closed non-contact syringe-driven and sensor controlled dispenser that addresses these limitations.

WORKING PRINCIPLE

The presented system in this paper is a non-contact syringe-driven and sensor controlled dispenser. The concept, like depicted in Fig. 1 is similar to the well-known syringe-solenoid dispensers [3]. In contrast to these, the system presented here comprises - in addition to the driving syringe and the dispensing valve - an enclosed gas volume (denoted as V_{gas} in the following). The gas volume is in fluidic contact with a presser sensor attached through a T-connector. The dimensions of the connection channel assure that the gas volume forms a stable meniscus between sensor and liquid, such that liquid never gets in contact with the sensor and the sensor is not contaminated. While the pressure sensor is used to measure the pressure of the enclosed gas volume, the syringe serves as reservoir and pressure source when actuated by the linear drive mechanism.

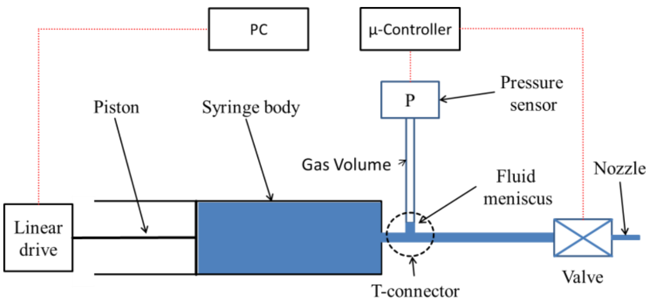

Figure 1: Schematic of the sensor controlled dispenser showing the different parts of the device.

In order to eject liquid out of the system, a positive pressure difference is created between the inside of the syringe and the surrounding environment. A linear drive is therefore used to push the piston which leads to compression of the enclosed gas volume V_{gas}. Except of the enclosed gas volume, the process is exactly the same like in conventional syringe-solenoid systems. However, the continuous monitoring of the pressure with the sensor, enabled by the presented setup, allows for a precise control of the movement of the linear stage. The movement can be stopped precisely when a predetermined pressure P_1 is reached inside the gas chamber.

Once the gas is pressurized, the valve can be opened to release the liquid through the nozzle. The liquid is then driven out of the nozzle by the pressure difference P_1 between the inside of the syringe and the surrounding pressure of the environment. As soon as the fluid moves, the gas pressure begins to drop and the gas volume increases accordingly. An approximate relation between the enclosed gas volume V_{gas}, the volume of ejected liquid V_{liq} and the pressure drop measured by the pressure sensor ΔP is given by the law of Boyle-Marriotte applied to the enclosed gas volume:

$$V_{liq} = V_{gas}\left(\frac{P_0 + P_1}{P_0 + P_1 - \Delta P} - 1\right) \qquad (1)$$

Where P_0 is the environmental pressure in the lab. Though, equation (1) is not considering dynamic effects while the liquid is flowing, it holds for the steady state, i.e. after closing the valve the relation of the quantities in equation (1) is exact. Based on this a simple 0^{th}-order control can be established: To control the dispensed volume the user has to choose a defined pressure drop to be established by the device during the dispensing run i.e. after loading the syringe with a pressure $P_1 > \Delta P$, the valve has to open until the sensor indicates that the set pressure has been reached. Thus, the ejected volume of liquid is approximately given by equation (1) and the bigger the pressure drop the bigger the volume dispensed.

Figure 2 illustrates the working principle with a schematic curve of the pressure inside the gas chamber and shows how a typical dispensing event influences the pressure.

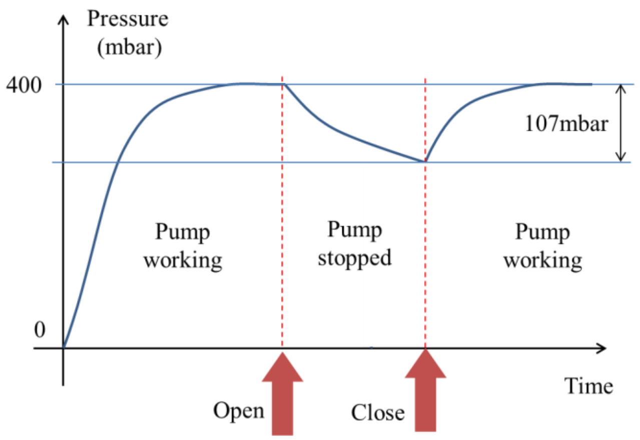

Figure 2: Typical signal during dispense (pressure difference 107 mbar). First the linear drive builds up the pressure by pushing the plunger into the syringe body. When the valve opens (first red arrow), the pressure (blue) drops until a certain pressure difference is reached; the valve is then automatically closed (second red arrow).

One important point that should be mentioned in the context of the description of the working principle is the complete absence of time control on the dispenser. Since only the physical state variables pressure and volume are related to each other (eq. (1)), moderate changes in fluid properties play no role in the control of the volume. Therefore, the dispensed volume of liquid is in principle independent of changes in viscosity or other fluidic properties.

MATERIALS AND SET-UP

The experimental setup used to study the described working principle is based on a commercial 20 ml syringe (Plastipak, BD). A T-connector (Festo) is fixed to the end of the syringe. One tube is attached to the pressure sensor RVAQ300GU (Sensortechnics), designed for measuring 0 to 400 mbar pressures with a sensitivity of 10 mV/mbar (Fig 3-A). The third end of the T-connector is connected to a normally closed piezoelectric valve (Vermes) having a 100 µm PEEK nozzle (Fig 3-B). The syringe and the tube connecting the valve are filled with the liquid to be dispensed, whereas the tube connecting to the sensor remains filled with air due to the dead end formed by the sensor. The defined volume V_{gas} is thus trapped between the liquid and the pressure sensor.

To avoid any capacitive effect inside the system, the individual components are chosen as stiff as possible. Therefore, during the compression only the gas volume inside the tube is changing and no significant expansion of the used plastic parts occurs.

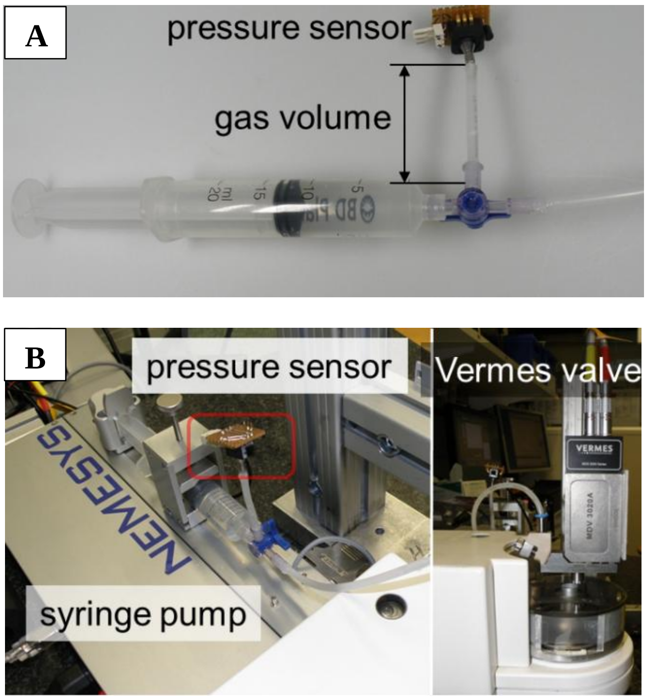

Figure 3: A - View of the syringe with an enclosed gas volume and pressure sensor attached. The other end of the tubing is connected to the valve. B - View of the mounted syringe on the linear drive (neMesys, Cetoni) (left side) and Vermes valve positioned over a microbalance (right side).

A PC-controlled linear drive (neMESYS, Cetoni) is used to move the plunger of the syringe and to build up the pressure inside the gas chamber until a pre-defined value (set-value) is reached. The measurement of the ejected volume of working fluid is done with ultra-microbalance (XP2U, Mettler-Toledo) placed under the nozzle of the valve (fig 3-B). The raw data of the balance is subjected to an evaluation algorithm taking into account effects of evaporation and other environmental factors to calculate the volume [4].

To increase the velocity of the dispensing and to avoid any time consuming communication with the PC, the handling of information coming from the sensor and the valve is realized within a micro-controller. It treats the pressure sensor signal in quasi real-time (approximately 100 µs response time) and executes the programmed loop to control the dispensing process.

EVALUATION OF THE DISPENSER

Proof-of-principle

This system is characterized with two different liquids, distilled water and Phosphate Buffered Saline (PBS), see Table 1. Both of them are often used in the IVD industry. Water is dispensed to cover the whole operating range (500 nl, 1 µl, 5 µl and 25 µl) whereas PBS is only dispensed at two pressure levels corresponding to 1 µl and 25 µl. Table 1 presents the physical properties of the two fluids used during these performance tests.

Table 1. Liquids used for experiments and their properties @ 20 °C.

Fluid	Density (kg/m3)	Viscosity (mPas)	Surface Tension (mN/m)
Water	998	1.03	71
PBS	1050	1.20	62

The dispenser was set up as shown in Fig. 3. We have chosen to operate the system at the maximum pressure reachable with our pressure sensor (P_1 = 400 mbar) in order to achieve a high Weber number (We) and therefore obtain a clean break-up of the jet. It is also important to have a sufficiently large range for ΔP available that always leads to jet ejection (i.e. We > 8) to cover the complete volume range.

In the experiments the pressure is built up inside the syringe to the desired initial value (P_1 = 400 mbar) by moving the linear drive. Each volume is investigated by one dispensing run composed of 48 individual dispensing events. Figure 4 provides an example of such a run. To obtain an ejected volume of about 470 nl with DI water a pressure drop of 2 mbar was required. A standard deviation of individual droplet volumes of 3.7 % was determined in this case (see Fig. 4).

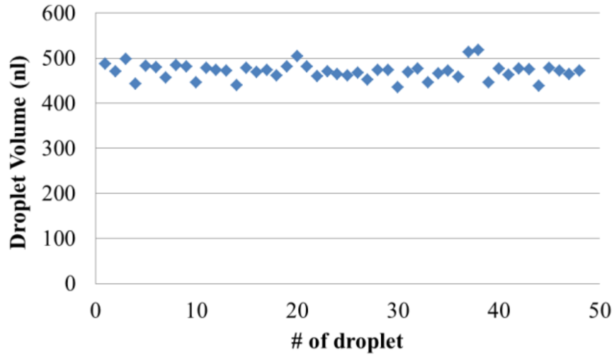

Figure 4: Results of 48 gravimetrically measured droplets of water at a mean volume of 470 nl and a standard deviation of 3.7%.

The total gas volume enclosed inside the dispenser was measured to be approximately 300µl. By using equation (1) it is thus possible to deduce the pressure drop corresponding to the volume dispense. Figure 5 shows the direct correlation between the measured volumes and the theoretical calculations for water based on the enclosed volume of 300µl. Except for small volumes/pressure-drops, the agreement between experiments and theory is very good (see also Table 2). The main reasons for discrepancies are mainly due to two major points:

1 - the signal to noise ratio of the pressure sensor is smaller for small pressure changes. Therefore, the measured results of pressure sensor is less accurate and therefore the dispensed volume, too.

2 - the dynamic increase of the pressure in the first milliseconds is really fast. Therefore, the latency of the micro-controller and/or the valve leads to the effect that the pressure still increases even after the valve was requested by the algorithm to be close.

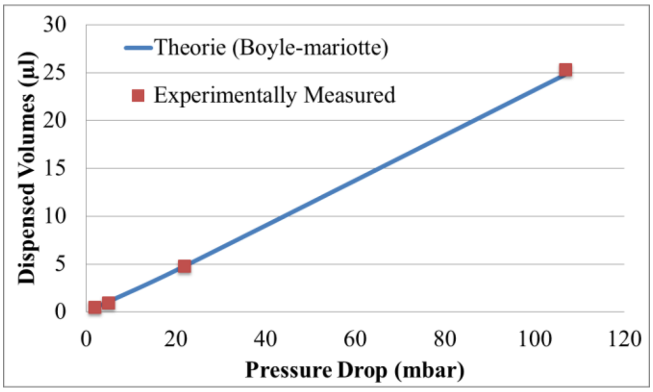

Figure 5: Correlation between equation (1) and ejected fluid volumes. The gas volume is taken as 300 µl and the maximum pressure inside the gas chamber is 400 mbar.

Performances

The performance of the system for the different liquids and volumes investigated is shown in Table 2. The minimum and maximum values used for ΔP are 2 mbar to dispense 500 nl and 107 mbar for 25 µl. Standard deviations between individual dispenses are between 1 and 5 %. The measured volumes match the expected volumes calculated in previous section.

Table 2. Summary of the different experiments for the two different liquids and their respective standard deviations. Volumes are calculated using the densities given in table 1. Theoretical volumes are calculated by equation (1).

Water – 400 mbar

Pressure difference (mbar)	Theoretical volume (nl)	Mean Volume (nl)	Standard deviation
2	430	467	3,7%
5	1075	952	4,2%
22	4790	4804	2,2%
107	24825	25285	1,5%

PBS – 400 mbar

Pressure difference (mbar)	Theoretical volume (nl)	Mean Volume (nl)	Standard deviation
5	1075	1077	4,6%
107	24825	24596	0,7%

These results prove the capacity of the proposed sensor controlled system to work with different liquids and a large range of volumes without calibration or any change of the setup. Simply, the measurement of the pressure drop by the applied sensor allows for addressing the whole volume range. The dispense time of course varies along with the volume as well as with the viscosity. In our experiments the dispense time was between 5 ms for 500 nl and 250 ms for the 25 µl.

Optimization potential

One limitation of the presented approach is the large actuation pressure required, in order to obtain clean and precise droplet break-up for all dispensed volumes in the considered range. In contrast to this, the pressure drop needed to address the sub-microliter range is really small. Therefore, a pressure sensor with high burst pressure and large dynamic range is required, if the addressable volume range is to be increased.

The trapped gas volume can also be subject to optimization: A small volume will allow a more precise control in the sub-microliter range, but then will prevent to dispense large quantities in a one-step. However, within this frame, the presented setup can be easily adapted to different user requirements in terms of volume range by simply selecting an appropriate gas volume and corresponding sensor type. Furthermore, the control algorithm could be further refined to take also dynamic effects neglected in equation (1) into account. Such dynamic flow effects during jet ejection might be the cause for the reduced accuracy of PBS at low volume (cf. Table 2).

Two other environmental limitations of the system exist due to its dependence to the Boyle-Mariotte law. First important changes of laboratory temperature during the use of the system will lead to inaccurate and imprecise dispensing. Second the solubility of air in water is increased by 40% when the pressure is increased by 400mbar. If the system is used over a long period of time, the total gas volume V_{gas} and the dispensed volume will both become smaller as expected.

CONCLUSION AND OUTLOOK

The presented system demonstrates the feasibility and good performances of a non-contact normally closed and pressure regulated smart dispensing system to deliver small aliquots of different liquids without calibration. Future work will be dedicated to the improvement of this system to obtain better accuracy and precision and to cover efficiently an extended range of viscosities and volumes. This may include a better pressure sensor allowing the measurement of larger pressures and also a better precision. Such modifications can help to address the briefly described optimization potential of this dispensing technology.

ACKNOWLEDGMENT

The authors gratefully acknowledge financial support from the German Federal Ministry for Science and Education (BMBF) through the project “Smart Reagent Dosage” (SFK 16SV5119).

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