Dokuz Eylül Üniversitesi Mühendislik Fakültesi Fen ve Mühendislik Dergisi
Dokuz Eylul University Faculty of Engineering Journal of Science and Engineering
Elektronik/Online ISSN: 2547-958X

RESEARCH ARTICLE / ARAŞTIRMA MAKALESI

Development of an Automatic Liquid Dosing System in Microliter Scale

Mikrolitre Ölçeğinde Otomatik Sıvı Dozajlama Sistemi Geliştirilmesi

Abstract

The goal of this study is to design a novel automatic liquid dosing system for liquid sampling at the microliter level. For this purpose, a mechatronics system is designed to position a syringe at the desired position in the workspace and then drive its piston to inject the liquid to be sampled. Then, an application-specific algorithm is developed to be able to prepare samples in 3x3, 4x4, and 5x5 sample container arrays with a desired volume. The performance tests are conducted for preparing samples with up to three different liquids. The repetitive experiments are performed for 50 and 100 µL sampling volumes. The results indicated that it is possible to dose a single liquid with the highest average deviation of 3.9%. Moreover, it is found that it is possible to prepare a sample with a mixture of three liquids by the highest average deviation from the reference value of around 3.4% when the targeting sampling volume is 250 µL for each liquid.

Keywords: *Automatic liquid dosing, liquid sample preparation, mechatronics system design, micro-dosing*

Öz

Bu çalışmanın amacı, mikrolitre seviyesindeki hacimlerde sıvı numunelerin hazırlanabilmesi için özgün bir otomatik bir sıvı dozajlama sistemi tasarımıdır. Bu kapsamda, belirlenen çalışma alanı içerisinde bir şırınganın pozisyonlandırılması ve içerisindeki sıvının boşaltılması için bir mekatronik sistem tasarımı yapılmıştır. Daha sonra, istenilen hacimlerdeki numunenin 3x3, 4x4 ve 5x5'lik numune kabı dizilimlerinde hazırlanabilmesi için uygulamaya özel bir algoritma geliştirilmiştir. Sistemin performansı, numune hazırlanması sırasında üç adete kadar farklı sıvılar kullanılabilecek şekilde test edilmiştir. 50 ve 100 µL numune hacimleri için tekrarlı deneyler gerçekleştirilmiştir. Elde edilen sonuçlar bir adet sıvının, en fazla %3.9'luk bir ortalama sapma ile dozajlanabileceğini göstermiştir. Ayrıca, testler üç farklı sıvı kullanılarak numune elde etmenin mümkün olduğunu göstermiştir. Bu durumda, her bir sıvıdan 250 µL'lik bir hacim alınarak oluşturulan numunenin, referans olarak verilen hacimden en fazla %3.4'lük bir ortalama sapmaya sahip olduğu gözlemlenmiştir.

Anahtar Kelimeler: *Otomatik sıvı dozajlama, sıvı numune hazırlama, mekatronik sistem tasarımı, mikro dozajlama*

1. Introduction

Technological advancements have led to an increment in the number of engineering devices operating for small-scale handling processes. One of them is the handling of liquids for various purposes [1]. Concerning them, liquid dosing in small amounts is an important concern for numerous applications such as sample preparation [2], point-of-care diagnostics [3], 3D printing [4], inkjet printing [5], etc. Among them, one of the most important is sample preparation for laboratory tests. The main problem in this application is possible volumetric errors due to the conventional manual pipetting of each sample especially in small volumes [6]. Moreover, they are mostly requiring the combination of more than one chemical [7]. This leads the volumetric errors to propagate further for the mixture. To avoid and overcome these errors, many researchers focused on various liquid dosing devices [8]. These devices are mainly driven by piston-like structures [9], piezoelectric actuators [10], pneumatic generators [11], acoustic devices [12], and peristaltic pumps [3].

One of the earliest attempts at liquid dosing in small volumes was made by Lammerink et al. [13]. They combined a thermo-pneumatic actuator and a flow sensor to provide a closed-loop concept for the process. They focused on the continuous liquid flow with a controlled amount. Their results indicated that it is possible to achieve a flow range within 0-50 µL/min. Streule et al. [14] developed a liquid dosing system called "Pipe-jet" which is actuated by a piezo stack-driven piston. They tested samples with different viscosities within the microliter level. According to the findings, they achieved successful dosing with a coefficient of variation of less than 2%. Lake et al. [15] designed a syringe pump for microfluidics applications. PID and bang-bang controllers were implemented to control the amount of the transferred liquid. The results showed that the reference pressure value can be obtained within the deviations of ±1% and ±5% for PID and bang-bang controllers, respectively. Carvalho et al. [16] developed an autosampler called "OSMAR" which is driven by two combined G-code machines. The system is suitable to handle both liquids and gases with its low-cost design. Their observations confirmed that the system can handle air at the microliter level. The movement precision of the setup was lower than 1%. Samokhin et al. [17] presented a syringe pump mechanism to dose liquids in the analytical laboratory. The

DOI:10.21205/deufmd.XXXX

Atıf şekli / How to cite:

SOYAD, AD. (2023) Makale adı. DEUFMD, XX (XX), XXX-XXX.

Geliş Tarihi / Received: XX.XX.2023
Kabul Tarihi / Accepted: XX.XX.2023

syringe pump is capable of both infusing and refilling the empty syringe. They dispensed the liquid in 1 and 5 mL volumes. Their findings revealed that the systematic error of the system was less than 0.1%. Florian et al. [18] built an automated system for micropipetting of liquids in a 3D workspace called "OTTO". The system was designed according to the requirement of speed and positional resolution for qPCR. They obtained a successful dosing with an average pipetting error of 2.5%. Barthels et al. [19] proposed an automatic liquid handling system for life sciences applications. They used a commercial micropipet which is integrated with a displacement piston. They concluded that the system successfully dispenses the liquids with relative pipetting errors lower than 0.3%. Boppana et al. [6] developed an automated pipetting system for the microliter-level handling of liquids. The system consists of a single board computer, software interface, dual syringe pump, and plunger positioning system. They reported that the accuracy of the system was determined between 98 to 102% and the relative standard deviation was less than 3%.

In perusing the available literature, it is seen that there are many efforts regarding the handling of liquids with different purposes. However, the requirement for novel designs still exists for sampling purposes within an automated technique [20]. This need is more significant, especially in the case of preparing samples in batches with considerable accuracy and precision [21]. In this study, we developed and implemented a mechatronics system that provides an automatic liquid dosing for sample preparation. For this, we first designed a 4-DOF mechanism which is actuated by stepper motors. Then, we integrated a syringe substitution module for changing the syringe for different types of liquids. The system can prepare samples consisting of up to three different liquids without any contamination. Also, the system is adaptable to a varying number of samples within its workspace.

2. Materials and Methods

2.1. Definition of the Problem

Before the design of the mechanical system, it is important to understand the injection of the liquid from the syringe under an applied pressure. Figure 1 depicts the schematic of a single syringe with the given geometrical parameters. Also, the figure includes the required piston pressure (P_p) demonstration combined with the head loss terms.

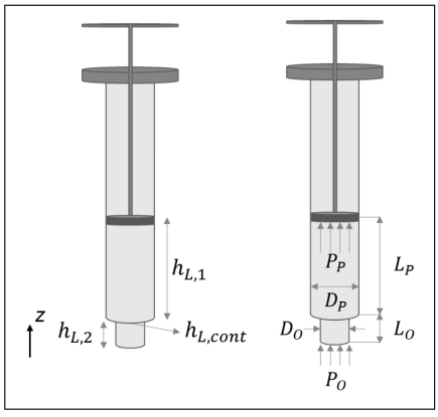

Figure 1. Schematic of a single syringe including geometrical parameters (not scaled), pressure, and head loss terms.

By employing the general energy balance, the required piston pressure (P_p) to dose the liquid can be written as follows [22]:

$$P_p = P_o + \frac{1}{2}\rho\left(V_o^2 - V_p^2\right) - \rho g\left(\Delta z - h_{L,1} - h_{L,2} - h_{L,c}\right) \quad (1)$$

where P_o is the atmospheric pressure, ρ is the density of the liquid, V_o is the velocity of the liquid at the outlet of the injector, V_p is the velocity of the piston, Δz is the elevation difference between the piston end and the injector tip, $h_{L,1}$ is the head loss through the syringe, $h_{L,2}$ is the head loss through the injector and $h_{L,c}$ is the head loss due to the sudden contraction from syringe to the injector. In Eq.1, the head loss terms are expressed as [23]:

$$h_{L,1} = f_p \frac{L_p}{D_p}\frac{V_p^2}{2g} \quad (2)$$

$$h_{L,2} = f_o \frac{L_o}{D_o}\frac{V_o^2}{2g} \quad (3)$$

$$h_{L,c} = K_{L,c}\frac{V_o^2}{2g} \quad (4)$$

where L_p is the distance between the piston and syringe inner surfaces, L_o is the length of the injector, D_p is the piston diameter, D_o is the injector diameter, f_p, and f_o are the friction factors for piston and injector sides and can be found for each side as [23]:

$$f = \frac{64}{Re} \quad (5)$$

where Re can be calculated by:

$$Re = \frac{\rho V D}{\mu} \quad (6)$$

The loss coefficient for sudden contraction in Eq.4 can be determined as [23]:

$$K_{L,c} = \alpha\left(1 - \frac{D_o^2}{D_p^2}\right) \quad (7)$$

In Eq.7, α is the kinetic energy correction factor. Assuming the liquid employed in the syringe is nearly incompressible, the relation between the velocity of the piston and the liquid in the injector can be expressed as follows [24]:

$$V_o = V_p\frac{A_p}{A_o} \quad (8)$$

where A_p and A_o are the cross-sectional areas of the piston and injector, respectively. By considering Eqs.2-7, Eq.1 can be rewritten as:

$$P_p = P_o - \rho g\Delta z + \frac{32\mu\left(L_o + L_p\right)}{D_p^2}V_p + \frac{1}{2}\rho\left[\left(1 + \left\{\alpha\left(1 - \frac{D_o^2}{D_p^2}\right)^2\right\}\right)\left(\frac{D_p^4}{D_o^4}\right) - 1\right]V_p^2 \quad (9)$$

Eq.9 depends on the liquid properties and geometrical parameters. Hence, if they are determined as the design criteria, a relation between the velocity of the piston and the pressure applied to the piston can be built. Herein, we employed a syringe with L_p=75 mm, L_o= 80 mm, D_p=8.8 mm, and D_o=0.9 mm. In the case of using water (ρ=998 kg/m³ and μ=0.001 Pa·s), the

maximum absolute pressure required and flow rate depending on the piston velocity are estimated.

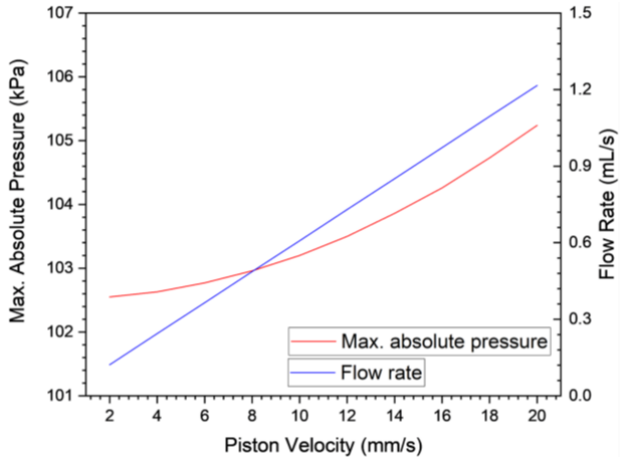

Figure 2. Variation of the maximum absolute pressure and flow rate depending on the piston velocity.

Figure 2 indicates that the piston velocity values between 2-20 mm/s results in a maximum absolute pressure requirement range of 102.5-105.2 kPa and flow rate range of 0.12-1.22 mL/s. To generate these pressure levels regarding the controlled motion of a piston and position the syringe through a sample container array, we developed a 4-DOF mechanism.

2.2. Mechanical Design

Figure 3a depicts the computer-aided design of the automatic liquid dosing system (ALDS). The system consists of a base that is constructed by sigma profiles and four chrome round bars. Then, two more chrome round bars are mounted to the base via four 3D-printed components including linear ball bearings for each. Also, four step motors are utilized and attached to the 3D-printed components, and thanks to the belt and pulley structure (Figure 3b), the system becomes able to provide a plane motion. Following, a syringe position unit (SPU) is assembled to the two chrome round bars with four more linear ball bearings. Therefore, SPU is adapted to be positioned in the plane.

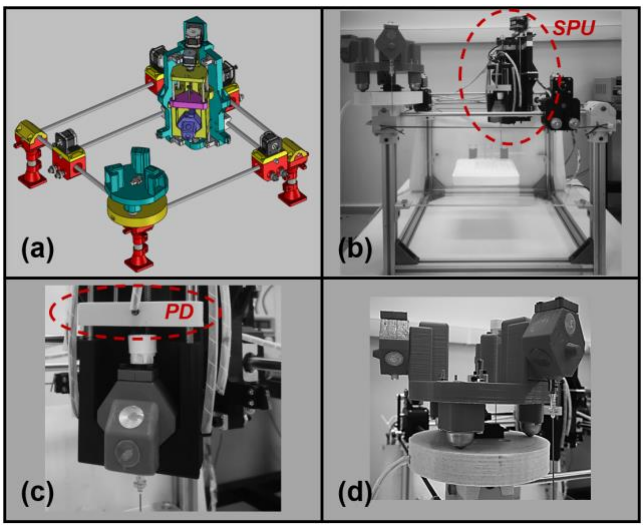

Figure 3. (a) CAD of the mechanism, (b) overall view of the mechanism (c) piston driving unit, and (d) syringe substitution unit.

The SPU includes two step motors, and they are coupled with ball screws to convert rotational motion into linear motion. The first motor is employed to position the syringe, and the second one is utilized to position the piston of the syringe (Figure 3c). The motions during both syringe and piston positioning are guided by chrome round bars. In the given configuration of the mechanism (Figure 3), it is easy to drive the piston downwards to release the liquid from the syringe, but it is not possible to drive the piston upwards to take the liquid inside the syringe. To make this possible, a ferromagnetic material is mounted to the top of the piston, and an electromagnet is placed on the piston driver (PD). Also, the syringe is kept inside a syringe holder component including three ferromagnetic components. Hence, when it is desired to fill the syringe with liquid, the electromagnet is activated, and magnetic force is used during upward piston motion. Finally, a syringe substitution unit (SSU) is implemented in the system to avoid contamination during sampling via more than one liquid. It is mounted on the corner of the base with three syringes with their holders. To automatically change the syringe with its holder, two permanent magnets are located inside the SSU for each syringe holder, and an electromagnet is located in the SPU. By activating the electromagnet during the sampling process, the syringe with its holder is kept on SPU. When it is required to be substituted for the next liquid, SPU is positioned near SSU, and the electromagnet is deactivated. Therefore, the permanent magnets on SSU attracted the syringe with its holder. Then, SSU is rotated partially via a servo motor, to align the next syringe with its holder. The electromagnet is activated once more, and its magnetic force overcomes the magnetic force of the permanent magnets. So that the positioning of the syringe and its piston is automatically provided with the given mechanism.

2.3. Electronics Design

The electronics design to control the motion of the motors and electromagnets is shown in Figure 4. The components that are utilized in the design are an Arduino Mega microcontroller, a Ramps 1.4 hardware controller, five Nema 17 step motors, a Nema 14 step motor, four motor drivers, two 12V electromagnets, two 24V electromagnets, eight limit switches, a servo motor, and two fans.

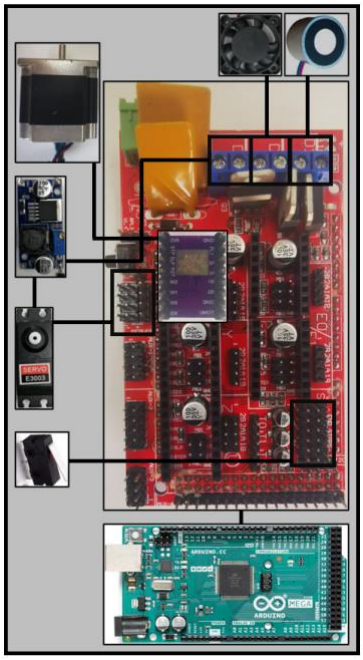

Figure 4. The schematic of electronics components of the system including microcontroller, control card, motor driver, step motor, servo motor, limit switch, voltage regulator, fan, and electromagnet.

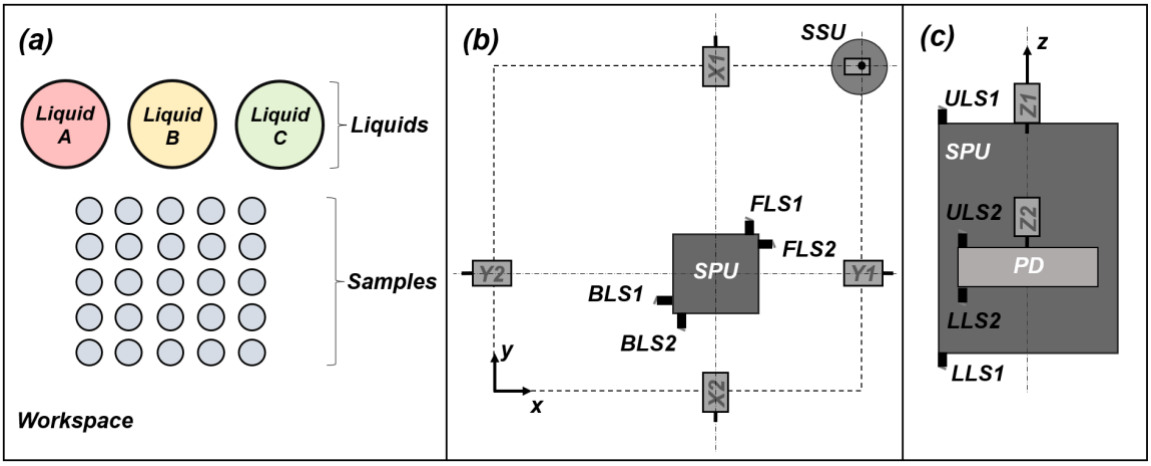

Figure 5. (a) Demonstration of the workspace including the positions of the liquids to be sampled and the samples within a 5x5 array. (b) Schematic of the workspace for the x-y plane motion including positions of step motors, servo motor, limit switches, SPU, and SSU. (c) Schematic of the SPU region including step motors, limit switches, and PD.

The operation of the system is controlled with Ramps 1.4 hardware controller combined with the Arduino Mega microcontroller. Four Nema 17 step motors are used for the movement of the SPU in the workspace. Then, the position of the syringe and its piston in SPU is provided by a Nema 17 and a Nema 14 step motor, respectively. As shown in Figure 4, limit switches are connected to the pins of the hardware controller to detect the different reference points of the mechanism as the initial position of the SPU, position of the SPU during the syringe substitution, lower and upper limits of the syringe and piston positions. A servo motor is also driven by the hardware controller in the SSU and to power it 5V, a voltage regulator is implemented. To attract each syringe holder from the SSU, two 12V and a 24V electromagnet are used inside the SPU. Also, another 24V electromagnet is used for keeping the contact between the top of the syringe piston and the SPU unit. To drive the 12V electromagnets power is directly supplied from the hardware controller. For the 24V electromagnets, a voltage regulator is employed. Moreover, two fans are used to remove the heat dissipated from electronic components.

2.4. Dosing Algorithm

The proposed mechanism is capable of preparing samples from three liquids without any contamination in its current structure. The schematic of the workspace designed for sampling is depicted in Figure 5a. As is seen from the figure there are two main regions available. The first region includes the liquids to be taken for sampling. The second region is comprised of the samples to be prepared by three different liquids. The schematic includes a demonstration of a 5x5 array of the sample containers. However, the numbers of the sample containers in the array can be adjusted.

To show the motion in the x-y plane, a schematic is also presented in Figure 5b. The origin of the coordinate system in the figure demonstrates the initial reference position for the SPU. *X1-X2* and *Y1-Y2* represent the step motors in corresponding directions. The position of the SSU is also shown in the corner of the workspace. In the figure, BLS and FLS denote the back limit switch and front limit switch, respectively. To detect the reference for the initial position and the syringe substitution position two limit switch couples are located on the SPU as *BLS1-BLS2* and *FLS1-FLS2*, respectively. Figure 5c depicts the SPU region including PD. As is seen from the figure *Z1* motor is used to position the SPU, and the *Z2* motor is used to position PD in the z direction. Herein, ULS and LLS denote the upper limit switch and lower limit switch, respectively. Therefore, to detect the upper and lower limits of the SPU and PD, *ULS1-ULS2* and *LLS1-LLS2* switches are employed.

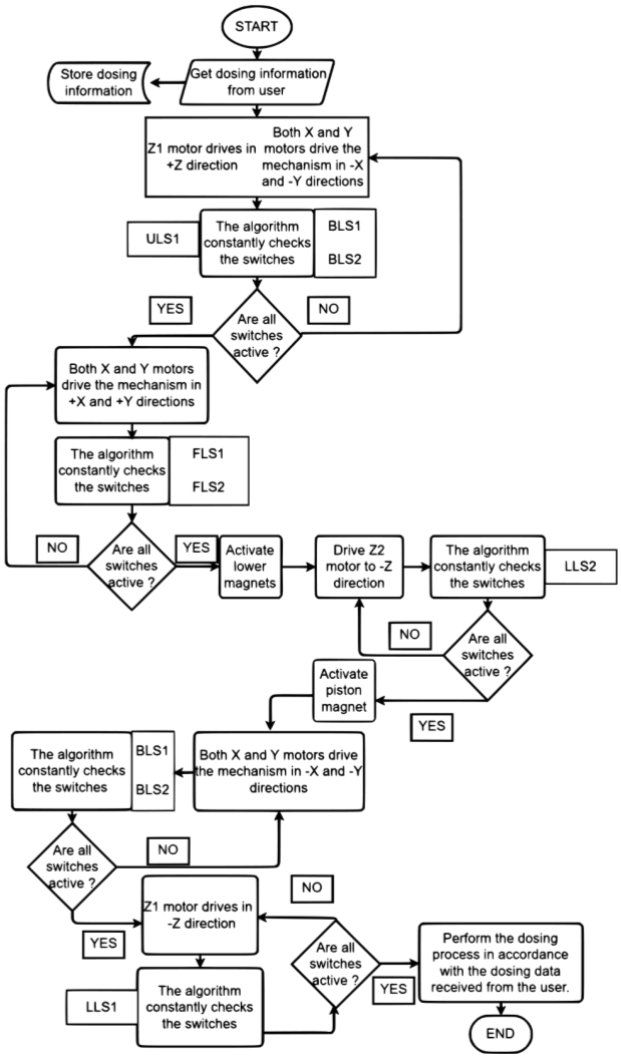

Figure 6. Flowchart of the algorithm of the automatic liquid dosing system.

The flowchart for the algorithm of the automatic liquid dosing system is shown in Figure 6. At the initializing of the process, the dosing information including the number of samples, positions of the samples, sample container height, and the liquid amount from each liquid is defined by the user. Then, the SPU is moved in -x and -y directions to reach the reference initial position. Simultaneously, SPU is moved in the +z direction by the *Z1* motor to achieve the upper limit of it. When *BLS1*, *BLS2*, and *ULS1* are enabled, it means the system is at the initial reference point and ready for the syringe-taking process. Then, the SPU is moved in +x and +y directions until *FLS1*, and *FLS2* are enabled which means that the SPU is positioned in front of the SSU. At that moment, the electromagnets on the SPU are activated and the syringe holder is taken with the help of magnetic force generated by them. Following, PD is moved -z direction by the *Z2* motor until *LLS2* is enabled. When *LLS2* is enabled, the electromagnet attached to the PD is activated. Hence, the connection between the syringe piston and the PD is provided. After that, SPU is moved in the -x and -y directions to reach the reference initial position again. After reaching this reference point, the *Z1* motor moves the SPU in the -z direction until *LLS1* is enabled. Depending on the height of the sample containers, the *Z1* motor moves the SPU in +z direction at a certain step defined by the user. Then, dosing starts regarding the defined information by the user at the beginning of the operation. First, Liquid A is taken into the syringe, and then it is extracted to each sample container with the pre-defined amount by controlling the step size of the *Z2* motor. After the sampling of Liquid A is completed, the same cycle is repeated for Liquid B and Liquid C.

3. Results and Discussion

During the experiments the piston velocity is fixed to 12.5 mm. As is seen from Figure 2, this corresponds to 103.6 kPa maximum absolute pressure requirement and 0.76 mL/s flow rate. It is observed that the developed mechatronics system can provide this pressure requirement in the tests. In this operation condition, the *Re* numbers are calculated as 110 and 1073 for piston and injector regions, respectively. To evaluate the performance of the system, first, the position of the injector tip without sampling any liquid is investigated. During this test, a 3x3 array is utilized which corresponds to nine samples. Positions of the sample containers are determined, and a marker is assembled to the SPU instead of a syringe. Then the system is operated regarding nine samples in a 3x3 array. Therefore, nine points are marked in the workspace. By comparing these marked points with the true positions of the sample containers, a positioning error is determined for each of them.

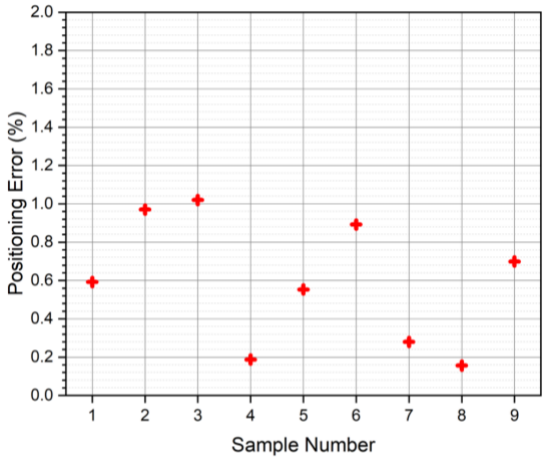

Figure 7. Positioning error (%) of the injector tip for 3x3 sample array.

The positioning errors for the injector tip in the workspace are shown in Figure 7. The positioning errors are calculated by considering the distance from the initial reference point. As is seen from the figure, the maximum positioning error appears around 1% and the average positioning error is found to be 0.6%. In the workspace, we used containers with square cross sections of 10 mm x 10 mm. The maximum positioning error corresponds to a deviation of around 1.2 mm. This means that the obtained positioning error does not affect the sampling process, because it stays in the error margins regarding the sample container dimensions.

Figure 8(a)-(c) depicts the experimental results for two different volumes of 50 and 100 µL. In these experiments, the dosing is made for only one liquid with three repetitions, and they are denoted in the figures as Exp1, Exp2, and Exp3. Also, this procedure is applied for three different sampling arrays of 3x3, 4x4, and 5x5 samples. As is seen from Figures 8(a)-(c), it is possible to dose the liquid precisely with the proposed dosing system. However, it is clearly seen from the figures that the volume of the first sample is considerably lower than the reference value in all cases. This is due to the dead volume of the syringes, which causes a bubble injection inside the syringes during the liquid intake process. This bubble is extracted in the first sampling, where the discharged liquid amount becomes lower. Regarding this observation, we considered the first sample as the outlier, and we did not include them in the accuracy and precision evaluation.

As the performance criteria in the dosing test the average deviation definition is employed as:

$$Average\ deviation = \frac{1}{N}\sum_{i=1}^{N}|x_i - x| \qquad (10)$$

where N is the data number, x is the true value, and x_i is the value of each data.

Figure 8(a) indicates the dosing within a 3x3 array. In this case, the average deviation from the reference values is found as 1.9% and 2.8% for 50 and 100 µL, respectively. Moreover, it is observed that 67% of the data is in the ±5% range for both 50 and 100 µL. Figure 8(b) depicts the dosing within a 4x4 array. The result in the 4x4 array indicated an average deviation from the reference values of 3.1% and 3.7% for 50 and 100 µL, respectively. In terms of precision, it is found that 71% of the data is in the ±5% range for both 50 and 100 µL. Finally, the dosing results for the 5x5 array are presented in Figure 8(c). It is observed that there is an average deviation from the reference values of 3.6% and 3.9% for 50 and 100 µL, respectively. Besides, it is found that 76% and 78% of the data is in the ±5% range of the 50 and 100 µL, respectively.

According to the obtained results for three different sample arrays, it is possible to dose individual liquids with an average deviation from the reference lower than 4%. It is found that this deviation increases with increasing sample number in the workspace. Another finding is that the system is able to dose an individual liquid within ±5% error range up to 78% for the given cases. This repeatability is obtained for the sampling volume of 100 µL which means that 78% of the samples can be dosed with a maximum 5 µL deviation. When compared to manual dosing in laboratories, this deviation could be evaluated as very acceptable.

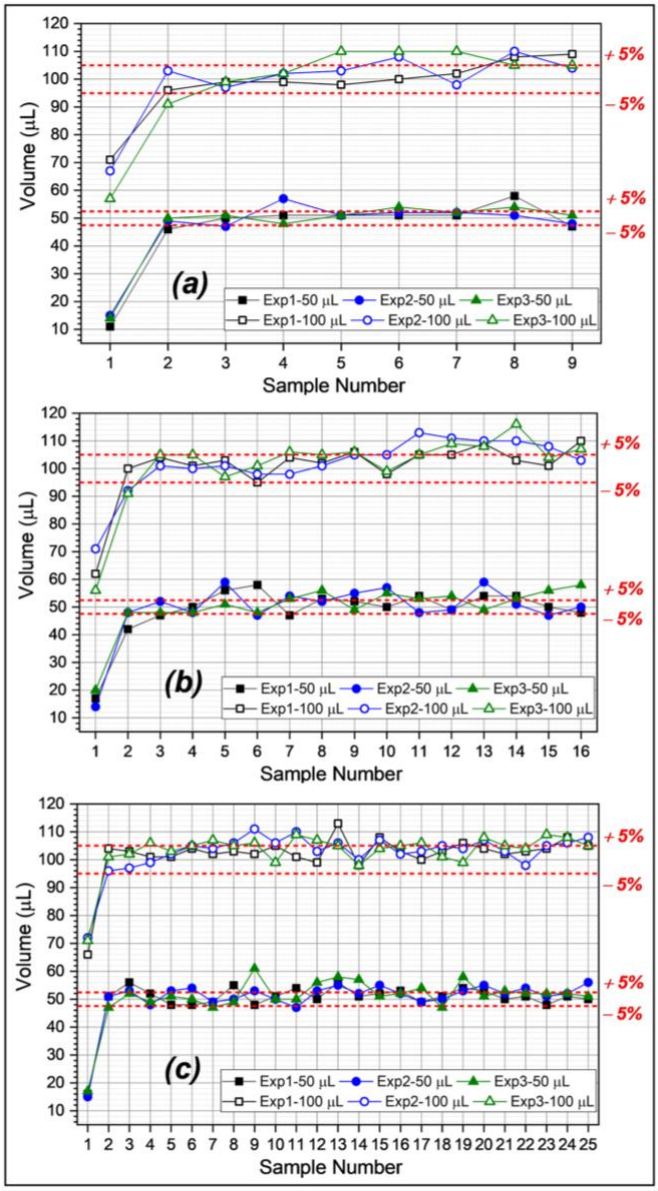

Figure 8. Dosing performance for two different volumes of 50 and 100 µL. Each experiment is conducted for one liquid with three repetitions in the cases of (a) 3x3, (b) 4x4, and (c) 5x5 sampling array.

To investigate the performance of the system during the preparation of a sample by mixing three liquids, the experiments are conducted for five different sampling volumes for each liquid between 50-250 µL. Herein, for instance, 50 µL from each liquid corresponds to a sample of 150 µL. During the preparation of the sample, first Liquid 1, then Liquid 2, and finally Liquid 3 is dosed to the container for each target sampling volume. Figure 9 reveals the results for five target sampling volumes where each color corresponds to a different liquid. It is seen from the figure that each liquid can be sampled accurately around the given reference value. The average deviations from the reference value are found as 1.9%, 2.8%, 3.4%, 3.4%, and 3.4% for 50, 100, 125, 200, and 250 µL target sampling volumes from each liquid, respectively. This implies that it is possible to prepare samples by the mixtures of three liquids is possible in different target sampling volumes with the proposed system. If we consider the maximum targeted sampling volume of 250 µL from each liquid, the average deviation becomes 3.4%. This means that there will be approximately a 25 µL average deviation during the preparation of a sample with 750 µL.

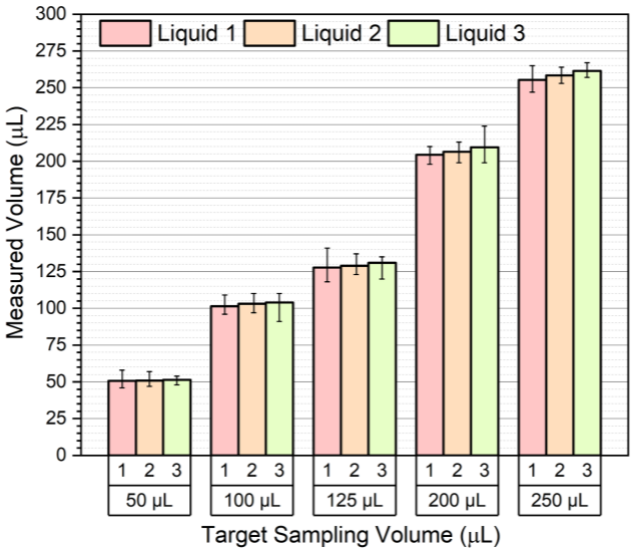

Figure 9. Dosing performance of the sample preparation with three different liquids. The sampling process is conducted by considering different volumes (50-250 µL) for each liquid. Error margins for each liquid and each target sampling volume are marked.

4. Conclusions

In this study, an automatic liquid dosing system is designed and tested for the preparation of samples in microliter-level volumes. For this target, a novel mechatronics system is designed and implemented with an application-specific algorithm. The following are the conclusions that can be drawn:

- The syringe can be positioned in the workspace with an error of around 1%.
- It is possible to conduct an accurate sampling process for a fixed volume. This case is tested for the lowest sampling volumes of 50 and 100 µL, and it is found that the highest average deviation is obtained for 100 µL in a 5x5 sample array as 3.9%.
- In terms of reproducibility, repetitive experiments are made for the lowest sampling volumes of 50 and 100 µL. In this experiment, it is obtained that up to 78% of the data is in the range of ±5% deviation range for a 100 µL sample in a 5x5 array.
- In the case of preparation of the samples with three different liquids, the highest average deviation is obtained when 250 µL is dosed from each liquid as 3.4%. This value decreases for the lower sampling volumes.

For future efforts, to increase the performance of the liquid intake process, mechanical design and the algorithm could be improved. Therefore, a possible bubble injection inside the syringes may be prevented. Moreover, a closed-loop control strategy could be implemented in the system to decrease the deviation from the reference volume and increase the precision of the sampling process.

Ethics committee approval and conflict of interest statement

The authors of this article declare that this article does not require ethics committee approval. The authors also declare that

this article has no conflicts of interest with any individual or institution.

Acknowledgment

Author Contribution Statement

References

[1] Councill, E., Axtell, N.B., Truong, T., et al. 2021. Adapting a Low-Cost and Open-Source Commercial Pipetting Robot for Nanoliter Liquid Handling, SLAS Technology, Vol. 26, p. 311-319. DOI:10.1177/2472630320973591

[2] Wu, Y.Q., Chen, H., Wang, W., He, N.Y., Liu B. 2016. Development and Validation of an Automated Liquid Handling System for Sample Preparation Based on Multichannel Air Displacement Pipetting Technology, Journal of Nanoscience and Nanotechnology, Vol. 16, p. 6867-6871. DOI:10.1166/jnn.2016.12597

[3] Behrens, M.R., Fuller, H.C., Swist, E.R., Wu, J.W., Islam, M.M., Long, Z.C., Ruder, W.C., Steward, R. 2020. Open-source, 3D-printed Peristaltic Pumps for Small Volume Point-of-Care Liquid Handling, Scientific Reports, Vol. 10, p. 1543. DOI:10.1038/s41598-020-58246-6

[4] Darling, C., Smith, D.A. 2021. Syringe Pump Extruder and Curing System for 3D Printing of Photopolymers, HardwareX, Vol. 9, p. e00175. DOI:10.1016/j.ohx.2021.e00175

[5] Roth, E.A., Xu, T., Das, M., Gregory, C., Hickman, J.J., Boland, T. 2004. Inkjet Printing for High-throughput Cell Patterning, Biomaterials, Vol. 25, p. 3707-3715. DOI:10.1016/j.biomaterials.2003.10.052

[6] Boppana, N.P.D., Snow, R.A., Simone, P.S., Emmert, G.L., Brown, M.A. 2023. Low-cost Automated Pipetting System Using a Single Board Computer and 3D-printing, Instrumentation Science & Technology, Vol. 51, p. 355-370. DOI:10.1080/10739149.2022.2129677

[7] Kong, F.W., Yuan, L., Zheng, Y.F., Chen, W.D. 2012. Automatic Liquid Handling for Life Science: A Critical Review of the Current State of the Art, JALA: Journal of the Association for Laboratory Automation, Vol. 17, p. 169-185. DOI:10.1177/2211068211435302

[8] Tsai N.C., Sue C.Y. 2007. Review of MEMS-based drug delivery and dosing systems, Sensors and Actuators A-Physical, Vol. 134, p. 555-564. DOI:10.1016/j.sna.2006.06.014

[9] Tashman, J.W., Shiwarski, D.J., Feinberg, A.W. 2021. A High Performance Open-source Syringe Extruder Optimized for Extrusion and Retraction During FRESH 3D Bioprinting, HardwareX, Vol. 9, p. e00170. DOI:10.1016/j.ohx.2020.e00170

[10] Englmann, M., Fekete, A., Gebefugi, I., Schmitt-Kopplin, P. 2007. The Dosage of Small Volumes for Chromatographic Quantifications Using a Drop-on-demand Dispenser System, Analytical and Bioanalytical Chemistry, Vol. 388, p. 1109-1116. DOI:10.1007/s00216-007-1335-7

[11] Cheng, S., Chandra, S. 2003. A Pneumatic Droplet-on-demand Generator, Experiments in Fluids, Vol. 34, p. 755-762. DOI:10.1007/s00348-003-0629-6

[12] Achim, W. 2006. Acoustically driven programmable microfluidics for biological and chemical applications. JALA: Journal of the Association for Laboratory Automation, Vol. 11, p. 399-405. DOI:10.1016/j.jala.2006.08.001

[13] Lammerink, T.S.J., Elwenspoek, M., Fluitman, J.H.J. 1993. Integrated Micro-Liquid Dosing System. IEEE International Conference on Micro Electro Mechanical Systems, February 10, Fort Lauderdale, 254-259. DOI:10.1109/MEMSYS.1993.296913

[14] Wolfgang, S. 2004. PipeJet: A Simple Disposable Dispenser for the Nano- and Microliter Range, SLAS Technology, Vol. 9, p. 300-306. DOI:10.1016/j.jala.2004.08.008

[15] Lake, J.R., Heyde, K.C., Ruder, W.C. 2017. Low-cost Feedback-controlled Syringe Pressure Pumps for Microfluidics Applications, PLoS One, Vol. 12, p. e0175089. DOI:10.1371/journal.pone.0175089

[16] Carvalho, M.C., Murray, R.H. 2018. Osmar, the Open-source Microsyringe Autosampler, HardwareX, Vol. 3, p. 10-38. DOI:10.1016/j.ohx.2018.01.001

[17] Samokhin, A.S. 2020. Syringe Pump Created Using 3D Printing Technology and Arduino Platform, Journal of Analytical Chemistry, Vol. 75, p. 416-421. DOI:10.1134/s1061934820030156

[18] Florian, D.C., Odziomek, M., Ock, C.L., Chen, H.N., Guelcher, S.A. 2020. Principles of Computer-controlled Linear Motion Applied to an Open-source Affordable Liquid Handler for Automated Micropipetting, Scientific Reports, Vol. 10, p. 13663. DOI:10.1038/s41598-020-70465-5

[19] Barthels, F., Barthels, U., Schwickert, M., Schirmeister, T. 2020. FINDUS: An Open-Source 3D Printable Liquid-Handling Workstation for Laboratory Automation in Life Sciences, SLAS Technology, Vol. 25, p. 190-199. DOI:10.1177/2472630319877374

[20] Torres-Acosta, M.A., Lye, G.J., Dikicioglu, D. 2022. Automated Liquid-handling Operations for Robust, Resilient, and Efficient Bio-based Laboratory Practices, Biochemical Engineering Journal, Vol. 188, p. 108713. DOI:10.1016/j.bej.2022.108713

[21] Tweed, J.A., Gu, Z.H., Xu, H., Zhang, G.D., Nouri, P., Li, M., Steenwyk, R. 2010. Automated Sample Preparation for Regulated Bioanalysis: An Integrated Multiple Assay Extraction Platform Using Robotic Liquid Handling, Bioanalysis, Vol. 2, p. 1023-1040. DOI:10.4155/bio.10.55

[22] Karimaghaee, P., Hosseinzadeh, A., Amidi, A., Roshandel, E. 2017. Adaptive Control Application on Syringe Pump Pressure Control Systems in Oil and Gas Industries. 5th International Conference on Control, Instrumentation, and Automation (ICCIA), November 21-23, Shiraz, 259-264. DOI:10.1109/ICCIAutom.2017.8258689

[23] Cengel, Y., Cimbala, J. 2013. Fluid mechanics fundamentals and applications (SI units). McGraw Hill, 1000s.

[24] Panton, R.L. 2024. Incompressible flow. John Wiley & Sons, 867s.