Evaluation of a microinjection system for severe dry eye treatment

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Abstract. This article presents the experimental results of a series of analysis and validation tests carried out on a microinjection system designed to deliver artificial tears to patients suffering of severe dry eye. The microinjector has the following characteristics: high efficiency and precision, user friendly, portable (8.5 x 4.5 x 2.5 cm) and low manufacturing and assembling costs. The microinjector overcomes many of the shortcomings inherent to the manual method drip, it has a syringe reservoir to keep and deliver the artificial tears. An electronically driven plunger pushes the solution into a capillary that transfer it to the patient’s eyes. The programmed time to deliver the tears fluid is set by the patient through a “C” program in an Android based device. The real delivering time differs slightly from the programmed one due to frictional effects between the plunger and the syringe walls. The validation tests had the objective to quantify the time difference between the programmed and real delivering times, using as artificial tears the Lagricel Ofteno brand, whis is the most used in Mexico. Two differentiable tests were done, in one test the plunger was lubricated with silicon oil (Ardes brand) for its compararation with the case where no lubricant is used. All test were done with an operating flow rate range of 0.13 - 60 (µL/min). The results show that the microinjection system has the ability to offer high performance and precision with ± 0.191 and ± 0.137 average error respectively for non-lubricated vs. lubricated tests.

The microinjection system can also be used for another compatible biomedical applications like chemotherapy, insulin administration, liquid drug delivery, among others adapting certain injection characteristics (flow rates and time).

1. Introduction

In persons with dry eye syndrome their lacrimal system does not adequately lubricate the surface of eye, presenting a wide variety of symptoms, usually characterized by a constant itching/burning sensation caused by the death of corneal epithelial cells, and a decrease in quality of the vision, among others. The reasons why dry eye syndrome occurs are usually of multifactorial origin, being aging and ethnic origin the most relevant.

Theefficientdelivery of ophthalmicsolutionsiscrucial in themedicaltreatmentofvarious eye diseases. Dry eye disease patients require varying amounts of commercially available drops of artificial tears which are manually administered throughout the day to achieve aqurate lubrication of the eyes [1]. The manual drip method is simple, but has significant drawbacks: it is tedious for the patient to dispense the drops in prescribed amount and time, drops volume is too large, generally only 1 to 10 % is
absorbed into the eyes [2]. Irregularity in patient compliance greatly compromises the efficacy of the treatment.

In recent years, several investigations have been carried out to design systems for the self-administration of ophthalmic solutions for the eyes. Semi-implants devices are placed partially under the skin [3], there are also implants inserted completely under the skin [4, 5] and devices placed in the conjunctival sac of the eye [6]. These devices that deliver ophthalmic solutions at a certain continuous basal rate over time, were developed to free patients from repeated self-administered injections and allow them to maintain an almost normal daily routine. Common disadvantages of these devices are: invasive, impractical, prone to contamination, and unsafe.

The study presented in this paper offers a solution to these problems by proposing a novel injection method that can be controlled by means of an android device using Wi-Fi. The proposed artificial teardrop microinjection system (shown in Figure 1) aims to help in the treatment of this syndrome, providing the patient with an electromechanical automated method for the continuous supply of tears on demand of the patient’s need. The electronic design, controlling program and a user guide of our device can be consulted in [7]. All device functions are automatically controlled remotely using a mobile app. The device has a capability of controlling the flow of tears to be injected, emulating the flow values produced by the human lacrimal system. The artificial tear fluid is transported from a reservoir inside the device to commissure of the eyelids through a flexible biocompatible microcapillary of 600/750 micrometers inner and outer diameters. The technical specifications of the artificial tears microinjection system are presented in Table 1. The dimensions of the device are $45 \times 25 \text{ mm}^2$ (Figure 1), which makes it practical for its transportation by the patient. Here we complemented the functionality and performance studies of our device by evaluating the time difference between the preprogrammed time and the one really taken by the device to deliver a required amount of fluid. The system guarantees a delivery of ophthalmic solution without altering its lubricating properties. It can be used for patients of all ages and will help in medical treatment for patients suffering from dry eye, eye infections and other eye diseases that are external or hospitalized that need constant treatment.

| Table 1. Specifications of the microinjector |
|--------------------------------------------|
| **Features**                               | **Range of values**                     |
| Operating mode                             | Periodic                                |
| Electric power                             | 9 V - DC (Rechargeable battery)         |
| Operating voltage                          | 5 V                                     |
| Flow adjustment range                      | 0.13 - 60 $\mu L/min$                   |
| Volume adjustment range                    | 0.0 - 2.0 mL                            |
| Operation time                             | $\sim$16.5 hours per day                |
| Time of refills / empty fortears reservoir | 30 seconds                              |
| Resolution                                 | 0.13 $\mu L/\text{Step}$                |
| Configuration panel                        | Possibility in many languages           |
| Ability to accept fluids                   | All solutions of artificial tears       |
| Temperature range                           | -20 at 60 °C                            |
| Weight                                     | 120 g                                   |

2. Materials and Methods

2.1. Materials

The materials needed to carry out the experiments and quantify the time precision of the microinjector are:
(i) The microinjector device described in [7] and shown in Figure 1
(ii) Artificial tears solution: Lagricel Ofteno
(iii) Ostwald viscometer: 0.7 \text{ mm} in diameter and 10 \text{ cm} in height
(iv) Thermal bath (Thermo Scientific TSSWB15)
(v) Stopwatch (1/100 s precision)
(vi) Silicone oil (Adres brand)

2.2. design Methods

The electronic of the miniaturized microinjector described in [7] has some delays between the preprogrammed and the real delivery time. It is one of the objectives of this study to explain the origin of these delays and quantify its relative importance. One of the possible sources of time error comes from the strong frictional forces between the plunger and the syringe’s wall, which have been measured and reported in [7]. The methodology designed to quantify the effects of friction consists in the realization of two different kind of tests, one using lubricating silicone oil between the plunger and the syringe’s wall and the other experiment without using lubricant. Then we compare the time needed to deliver a previously set amount of fluid between both experiments.

The application of the silicon oil on the surface of the plunger was made using a painter’s brush, taking care to cover homogeneously the whole surface and avoiding excess oil runoff. Once the plunger was covered in oil, it was placed inside the syringe and the microinjector was used to fill the reservoir with 1.0 \text{ mL} of artificial tears fluid using its “Fill reservoir” automated function. The same procedure was used to fill the non lubricated experiments. Then, different times were preprogrammed to deliver the ophthalmic solution and the differences between both sets of experiments recorded.

The time difference between these two experiments depends generally on the fluid viscosity. To establish the value for Lagricel Ofteno we used the Oswald viscometer following a standard procedure.

3. Results and discussions

The validation and performance tests with and without silicone oil were done under ambient conditions using air, distilled water, and Lagricel Ofteno artificial tears, which viscosity was measured in this work finding 0.054 \text{ Pa.s}, as test fluids. The programmed volumes vary from 120 to 1000 \text{ µL} and the injection times from 2 to 16.33 \text{ h}. For these tests, a silicon cylindrical capillary with an internal and external diameter of 600/750 \text{ µm} and 60 \text{ cm} long was used to emulate bringing the solution to the eye.

The results are indicated in Tables 2 and 3, the first and second columns indicate, respectively, the programmed volumes of fluid to deliver and the programmed time to do so.
found in the different columns are smaller, the microinjector delivered, for the three fluids, the programmed volume and the percentage error. Once again, regarding the time, the fourth and fifth columns globally titled “Air”, indicate, respectively, the time taken to the microinjector to deliver the programmed volume and the percentage error. Once again, within experimental error (1.0\%\%), there is no perceptible delay. For the case of distilled water, the sixth column indicates that a measurable delay is now present. The top row indicates, for example, that 1.0 mL was programmed to be delivered in 16 h 20 min, however the microinjector took 1 min 3 s longer, the time error being around 0.11 \%. As the viscosity increases the time delay is longer, as the last two columns for artificial tears show.

Table 2. Performance tests of the microinjection system with air, distilled water and Lagricel Ofteno without lubricating the rubber of the syringe

| P.V (µL) | P. T (h-m-s) | O.V (µL) | Air | Distilled water | Lagricel ofteno |
|----------|---------------|----------|-----|-----------------|-----------------|
|          |               |          |     |                 | (Ophthalmic solution 0.4\%) |
|          |               |          | R.T (h-m-s) | T.E (\%) | R.T (h-m-s) | T.E (\%) | R.T (h-m-s) | T.E (\%) |
| 1000     | 16-20-00      | 1000     | 16-20-00 | 0.000 | 16-21-03 | 0.100 | 16-21-30 | 0.153 |
| 960      | 16-00-00      | 960      | 16-00-00 | 0.000 | 16-00-43 | 0.070 | 16-01-31 | 0.157 |
| 780      | 13-00-00      | 780      | 13-00-00 | 0.000 | 13-00-37 | 0.070 | 13-01-16 | 0.162 |
| 600      | 10-00-00      | 600      | 10-00-00 | 0.000 | 10-00-29 | 0.080 | 10-01-07 | 0.186 |
| 360      | 06-00-00      | 360      | 06-00-01 | 0.004 | 06-00-32 | 0.140 | 06-00-51 | 0.236 |
| 120      | 02-00-00      | 120      | 02-00-04 | 0.055 | 02-00-07 | 0.090 | 02-00-18 | 0.249 |

With P.V: Programmed Volume; P.T: Programmed Time; O.V: Obtained Volume; R.T: Real Time and T.E: Time Error.

For table 2, the first result is in the third column “Obtained volume”, within experimental error (1 µL), the microinjector delivered, for the three fluids, the programmed volume without any problem. Regarding the time, the fourth and fifth columns globally titled “Air”, indicate, respectively, the time taken to the microinjector to deliver the programmed volume and the percentage error. Once again, within experimental error (1.0 s), there is no perceptible delay. For the case of distilled water, the sixth column indicates that a measurable delay is now present. The top row indicates, for example, that 1.0 mL was programmed to be delivered in 16 h 20 min, however the microinjector took 1 min 3 s longer, the time error being around 0.11 \%. As the viscosity increases the time delay is longer, as the last two columns for artificial tears show. For this case it took 1 min 30 s longer than the time programmed to inject 1.0 mL.

Table 3. Performance tests of the microinjection system with air, distilled water and Lagricel Ofteno with lubricating the rubber of the syringe

| P.V (µL) | P. T (h-m-s) | O.V (µL) | Air | Distilled water | Lagricel ofteno |
|----------|---------------|----------|-----|-----------------|-----------------|
|          |               |          |     |                 | (Ophthalmic solution 0.4\%) |
|          |               |          | R.T (h-m-s) | T.E (\%) | R.T (h-m-s) | T.E (\%) | R.T (h-m-s) | T.E (\%) |
| 1000     | 16-20-00      | 1000     | 16-20-00 | 0.000 | 16-20-27 | 0.045 | 16-21-03 | 0.107 |
| 960      | 16-00-00      | 960      | 16-00-00 | 0.000 | 16-00-19 | 0.032 | 16-01-04 | 0.111 |
| 780      | 13-00-00      | 780      | 13-00-00 | 0.000 | 13-00-13 | 0.027 | 13-00-57 | 0.121 |
| 600      | 10-00-00      | 600      | 10-00-00 | 0.000 | 10-00-12 | 0.036 | 10-00-48 | 0.133 |
| 360      | 06-00-00      | 360      | 06-00-00 | 0.000 | 06-00-00 | 0.000 | 06-00-37 | 0.171 |
| 120      | 02-00-00      | 120      | 02-00-00 | 0.000 | 02-00-00 | 0.000 | 02-00-13 | 0.181 |

In Table 3, a difference is observed with respect to the results in Table 2, the results found in the different columns are smaller, the microinjector delivered, for the three fluids,
the programmed volume without any problem. Regarding time, the fourth and fifth columns globally titled "Air" indicate, respectively, the time it takes for the microinjector to deliver the programmed volume and the percentage of error. Once again, within the experimental error, there is no delay, the system worked perfectly. In the case of distilled water, the sixth column indicates a little measurable delay. The top row indicates, for example, that 1.0 $\mu$L was scheduled to be delivered in 16 h 20 min, however, the microinjector took just 27 s compared to 1 min 3 s which was in the case without lubrication, with a time error of around 0.045 % as a reduction of 40 percent. The last two columns for artificial tears show a delay of 1 min 30 seconds, for the programmed time to inject 1.0 $\mu$L that presents a difference of 27 seconds in the case of the system operating without lubrication.

![Figure 2. Error graphic of programmed times for the Lagricel ophthalmic solution](image)

**Figure 2.** Error graphic of programmed times for the Lagricel ophthalmic solution

We clearly notice in Figure 2 the difference that exists on the functional level of the system by applying or not, the lubrication to the piston of the syringe. On the graph, the coordinate axis represents the programmed time error in percentage, to inject the amount of the lagricel ophthalmic solution and on the abscissa axis the programmed time. The blue bar represents the percentage of error committed over time without applying lubrication and the red bar indicates time errors when lubrication is applied to the system.

We can retain in these experiments that lubrication plays an important role in the functioning of the microinjection system, the advantage of which is to reduce the error of time to inject a very precise quantity to the patients. It observes on the graph for example at 16 h 20 min as the time programmed to inject 1 $\mu$L of ophthalmic solution of lagricel, that the time error committed when the system is lubricated, is reduced comparably to that whose lubrication has not been applied.

By analyzing these results, we can optimize the system reducing time errors by choosing a compatible material such as stainless steel in order to manufacture the transmission part of the movement connected to the motor allowing to overcome or break the friction force. Stainless steel is a recommended material for the manufacture of biomedical systems.

So in our next publications, we will present some experimental results using stainless steel as material for the manufacture of the transmission part of the movement.
4. Conclusions
In this work a set of experimental test were done to identify the origin of time delays of a miniaturized microinjector of artificial tears designed to help patients suffering from dry eye syndrome. It was found that the time delays increases with increasing viscosity of the test fluid. It was demonstrated that the frictional force between the syringe plunger where the ophthalmic solution is contained and the syringe’s wall is one of the main reasons for the temporal delay, since it decreases significantly when the plunger is lubricated with silicone oil. For the most viscous fluid tested (0.054 Pa.s) the average time delay error decreases from 0.191 % to 0.137% when the walls are lubricated with silicone oil. In any case, the microinjector delivers the eye’s lubricant with enough precision to relief patients problems. The comparison of the results obtained and the experience in the field of precise dosing of small amounts of solutions also indicate the need to optimize the system further to decrease any source of error to its maximum possible.

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