Preliminary Results in the Application of Ultrasound during the Injection of Drugs

Ruben Dario Muelas Ha., J. F. Pazos-Ospinaa, Gonzalo Fernando Casanova G., Joao L. Ealo a*

aVibration and Acoustics Laboratory. Mechanical Engineering School, Universidad del Valle, Calle 13 #100-00, Cali, 760032, Colombia

Abstract

During the injection of drugs into the brain a phenomenon known as backflow is presented, whereby the injected drug flows along the needle track rather than spread inside the target tissue. This backflow is a major problem because it produces an inadequate distribution of the drug. Previous studies have shown that backflow is dependent on some parameter such as the geometry of the needle, insertion speed and flow rate at which the infusate is injected. Also, this phenomenon is reduced when a radial compressive stress exists in the needle-tissue interface. In view of this, in this paper we propose an experimental setup to evaluate the effect of using ultrasonic wavefronts on the drug delivery distribution. A needle of 0.36 mm of diameter is coupled to a linear actuator which moves the needle at a speed of 0.5 mm/s in a phantom tissue sample of agarose gel. A single disk-like ultrasonic transducer with a through hole at its center to allow the insertion of the needle is used to generate the acoustic field. At the same time, a pump system injects a tracer inside the sample and makes visible the amount of liquid that is returned by effect of backflow. A numerical model of the acoustic field inside the sample is presented. Also, preliminary results with and without the application of ultrasound are discussed

© 2015 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: helical wavefront, acoustic vortex, phased array systems, multitransducer; spatial delays;

1. Introduction

Treatment for some neurological diseases such as epilepsy, Parkinson’s disease and brain tumors require more
effective techniques to deliver drug to the nervous system. Drugs delivery through bloodstream is a problem due to presence of blood-brain barrier, which is a cellular layer covering the inner space of blood vessels and avoiding the distribution of macromolecules from bloodstream to extracellular space of brain tissue [1]. Convection Enhanced Delivery (CED) is a technique where a needle is implanted into tissue and a constant flow rate or pressure is applied to deliver infusate directly to the target into the extracellular space [2]. Since dominant transport mechanism of this technique is convection, local drug distribution in higher volumes can be enhanced in comparison to dependent methods of diffusion [3]. However, a problem remaining in CED is backflow. This produces a non-adequate distribution of the drug inside the tissue, especially for high flows [4], since the fluid is distributed along the needle track instead of spreading over the region of interest [5]. This phenomenon is undesirable because medicine delivered may reach regions of the brain where it is ineffective, toxic and even cause serious side effects. Many of the factors influencing backflow are not still completely comprehended. It can be caused by local tissue damage, fluid-tissue interaction, or a combination of these both. During insertion of the needle, rupture of the brain tissue can create holes in the interface needle-tissue causing drug return. In this work we show preliminary results in the application of an ultrasonic pressure field to improve diffusion during drug delivery. A detailed description of the experimental setup implemented is included along with experimental results obtained when a tracer is injected into a brain-phantom sample.

2. Materials and Methods

The experimental setup implemented is intended to evaluate the back-flow generated in a phantom tissue sample of agarose gel and the potential effect of applying a ultrasound field when a tracer is injected. A brief description is presented below.

2.1. Agarose Gel

 Trevigel 5000 agarose gel powder was used. Agarose is a complex carbohydrate polymer extracted from seaweed that can be melted and dissolved in hot water. The preparation consisted in a 0.6 % concentration (weight/volume, w/v) corresponding to 6 gr per 100 ml of distilled water. Sealed and heated at 90-95 °C, for 15 minutes approximately, and finally poured into a mold for curing while it was cooled down to room temperature. Samples prepared were rectangular parallelepipeds of 47 mm width, 60 mm long and 18 mm of height.

2.2. Actuator and Syringe Pump

Actuator used was a stepper motor coupled to a linear way L or slider (model LWL7B-S2) to guarantee displacements in one direction. The actuator is excited by a DC-powered microstepping drive model (ST5-Q-NN) and programmable by software. It can be programmed using Q programming language. The distance, velocity and acceleration of the linear actuator are configurable by host commands executed from any PC. For infusion, a syringe pump model NE-300 (Artisan, USA) was used. It is configurable according to a diameter and rate limits. The syringe used in the setup was a BD-3mL with a maximum rate of 2.184 mL/min. The rate infusion of the tracer inside the phantom sample was selected to be 2uL/min.

2.3. Cannula and Tracer

A 28 gauge (0.36 mm diameter) blunt tip stainless steel needle was used. This kind of needle is used in clinical trials, and is commercially available. The tracer used was Evans blue dye. This allows perceiving clearly the diffusion effect inside the phantom tissue in presence of ultrasound waves.

2.4. Transducer

The ultrasonic emitter was designed and fabricated in our laboratory. It presents a cylindrical shape, 30 mm diameter and a thru hole, of 1 mm approximately at its center, through which the needle is inserted to the agarose gel samples. It operates at 1 MHz and was excited using a burst squared signal with 100 cycles and 100 Vpp.
2.5. Instrumentation Setup

The linear actuator was vertically placed on a metal frame. A bar was coupled to the motor in order to reach the sample that was positioned a distance of 30 cms approximately, where the needle was attached. The needle was connected to the syringe through a PEEK tube to inject the tracer to the sample. Insertion of needle inside the sample was at a linear speed of 0.5 mm/s and the target was located at 15 mm depth. To guarantee that the needle reached the target, it was firstly positioned on surface of the sample and then driven forward 15 mm. Once reached the target, the needle was stopped and paused 1 minute to allow tissue relaxation. Then, the tracer was injected at a rate of 50 μl/min a volume of 8 μl.

Given that we need to know how the diffusion inside the sample was in presence of ultrasonic fields, 3 different tests were performed. The first one consisted in injecting the tracer and wait 1 minute before extraction, without ultrasound application. In the second test, ultrasound transducer was turned on before the tracer was injected and it was turned off 30 seconds after the tracer finished infusion. The third test was similar to the first one but ultrasound was turned off once the needle was extracted. The experimental setup is summarized in Figure 1.

![Instrumentation setup](image)

Fig. 1. Instrumentation setup. (a) diagram and (b) picture of the system implemented.

3. RESULTS

3.1.1. Test 1 - Tracer without ultrasound

Once the needle reached target, a pause of 1 minute was taken before injecting tracer. And after injecting tracer 1 minute more was paused. After this, the needle was retracted and 2 minutes were recorded to analyze the diffusion process. In this time, no change was noticeable and the backflow was present along the needle track as shown in Figures 2(a) and 2(d).

3.1.2. Test 2 - Tracer with ultrasound during delivery

When the ultrasound was turned on while the needle was injecting the tracer, an almost immediate change in the color of the tracer was perceived. The tracer turned from violet to yellow. At the top of the needle, close to the sample upper surface, the dye almost disappeared. This change of color is assumed to be evidence that the concentration of tracer has been reduced by diffusion. See figures 2(b) and 2(e).

3.1.3. Test 3 - Tracer with ultrasound after needle extraction

The ultrasonic field was turned on just when the needle was absolutely out of the sample by a period of 30 seconds. The backflow did not have a noticeable change in color but on shape. It can be observed that the tracer along the needle track tends to increase its volume. Results are showed in Figures 2(c) and 2(f).
4. Conclusions

The experimental setup proposed allows observing the behavior of the tracer in presence of a ultrasound field. Changes in color and volume of the tracer are appreciated when ultrasound is applied, which indicates that tracer diffusion can be supported/modified.

Although only backflow effects with and without ultrasound are showed, the experimental setup enables us to study this phenomenon under different experimental conditions, such as changes in needle insertion speed, geometry of the needle, needle tip, etc.

Further research is required to develop a multiphysic model which includes: wave propagation, tracer diffusion and acoustic-needle interaction, which will allow us to estimate the effect of the ultrasonic field on tracer diffusion dynamics, prestress along the needle and backflow. Also, the effect of the probable vibration induced on the needle must be quantified. The application of a ultrasonic focused beam is also subject of further study.

Further research is required to develop a multiphysic model which includes: wave propagation, tracer diffusion and acoustic-needle interaction, which will allow us to estimate the effect of the ultrasonic field on tracer diffusion dynamics, prestress along the needle and backflow. Also, the effect of the probable vibration induced on the needle must be quantified. The application of a ultrasonic focused beam is also subject of further study.

References

1. F. Casanova, P.R. Carney, and M. Sarntinoranont. “Influence of Needle Insertion Speed on Backflow for Convection-Enhanced Delivery”. Journal of Biomechanical Engineering. Vol. 134. April 2012.
2. Allard, E., Passiraini, C., and Benoit, J.P. “Convection Enhanced Delivery of Nanocarriers for the Treatment of Brain Tumors”. Biomaterials, 30, pp. 2302-2318.
3. Rogawski, M.A. “Convection-Enhanced Delivery in the treatment of Epilepsy”, Neurotherapeutics, 6 (2), pp. 344-351. 2009.
4. Sampson, J. H., Archer, G., Pedain, C.,Wembacher-Schroder, E., Westphal, M, Kunwar, S., et al. “Poor drug distribution as a possible explanation for the results of the PRECISE trial”, Journal of Neurosurgery, 113, pp. 301-309. 2010.
5. Yin, D., Forsayeth, J., and Bankiewicz, K.S. “Optimized Cannula Design and Placement for Convection Enhanced Delivery in Rat Striatum”. Journal of Neurosc. Methods, 187, pp. 46-51. 2010.