Ocular drug delivery from contact lenses: mimetizing the hydrodynamic conditions of the eye

Andreia Pimenta[1,2], Ana Valente[1], José M.C Pereira[2], José C.F Pereira[2], Helena Filipe[3,4], José L.G. Mata[1], Rogério Colaço[2], Benilde Saramago[1], Ana Paula Serro[1,5]

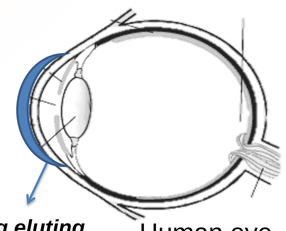
[1] Centro de Química Estrutural, Instituto Superior Técnico, University of Lisbon, Lisbon, Portugal
[2] Departamento de Engenharia Mecânica e IDMEC, Instituto Superior Técnico, University of Lisbon, Lisbon, Portugal
[3] Hospital das Forças Armadas - Polo de Lisboa, Lisbon, Portugal
[4] Hospital dos SAMS, Lisbon, Portugal
[5] Centro de Investigação Interdisciplinar Egas Moniz, Instituto Superior de Ciências da Saúde Egas Moniz, Caparica, Portugal

Introduction

Currently, most *in vitro* drug release studies for ophthalmic applications are carried out in static sink conditions. Although this procedure is simple and useful to make comparative studies, it does not describe adequately the drug release kinetics in the eye, considering the small tear volume and flow rates found *in vivo.*

In a normal situation, the human eye contains a tear volume that ranges from 6.2 to 30.0 μL [1] and the tear flow rate assumes values between 0.9 and 2.1 μL/min [2]. The use of contact lenses increases the tear turnover to values of the order 1.4-4.3 μL/min [2].

In order to predict in a more reliable way the drug release kinetics in the eye, it is crucial to develop microfluidic models that mimic, as close as possible, the hydrodynamic conditions of the eye.



Objectives

i) **Design** and validation of a **microfluidic cell** to **mimic** the continuous, volumetric flow rate of **tear fluid** and its low volume;

ii) **Comparison** of **drug release** profiles of anti-inflammatory, diclofenac (DCF), from a soft contact lens material obtained in **static sink** and in **dynamic conditions**;

iii) **Estimation** of the drug released *in vivo* **efficacy**.

Methods

① Microfluidic cell (MFC)

A MFC of poly(methylmethacrylate) with a cylindrical inner chamber of 45 μL was designed and fabricated.

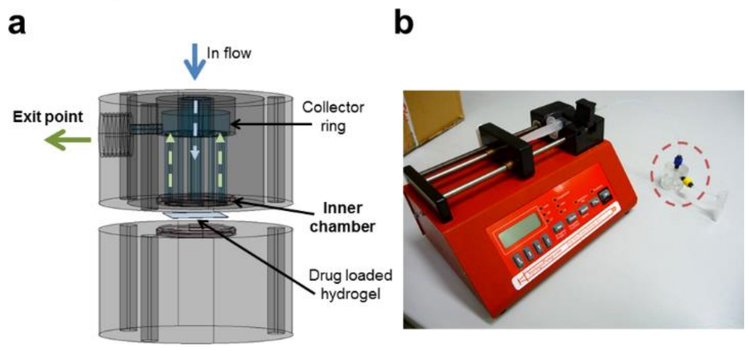


Figure 1.
a) Schematic design of the MFC
b) Experimental apparatus

The flow inside the microfluidic cell was modeled through the numerical solution of the Navier-Stokes and continuity equations using the Star-CCM+ simulation package.

② Drug release experiments

- *Static*: Diclofenac loaded 2-hydroxyethyl methacrylate (PHEMA) samples were immersed in 4 mL of PBS solution in closed vessels, at 36 °C, under stirring (180 rpm). At predetermined time intervals, 800 μl aliquots of the supernatant were collected and replaced by the same volume of fresh PBS solution.

- *Dynamic*: drug release experiments in the microfluidic cell were performed at 36°C and a continuous flow of PBS of 3 μL/min.

③ *In vivo* efficacy

The *in vivo* efficacy of anti-inflammatory released in dynamic conditions was estimated through comparison to the daily dose delivered by topical application.

Author contact: andreia.pimenta@tecnico.ulisboa.pt

Acknowledgments

To Fundação para a Ciência e a Tecnologia for Andreia Pimenta PhD grant BD/52334/2013 (MIT-Portugal program) and for funding through projects UID/QUI/00100/2013 and M-ERA.NET/0005/2012.

Results

⇨ MFC inner chamber with **volume of 45 μL**.

⇨ Considering a **flow rate of 3μL/min**, the fluid flows in the cell uniformly (Figure 2). Symmetric and very regular paths are followed from the inlet pipe to the eight exiting pipes.

➔ **Possibility of numerically simulate other inner chamber volumes and flow rates.**

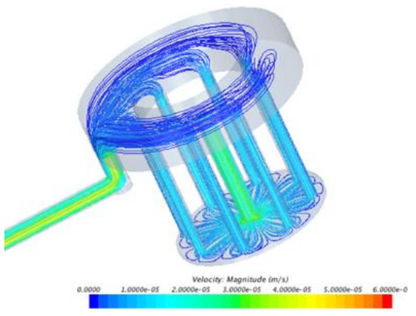


Figure 2. Representation of the fluid paths inside the microfluidic cell

➔ **Different release kinetics for the same drug/hydrogel pair.**

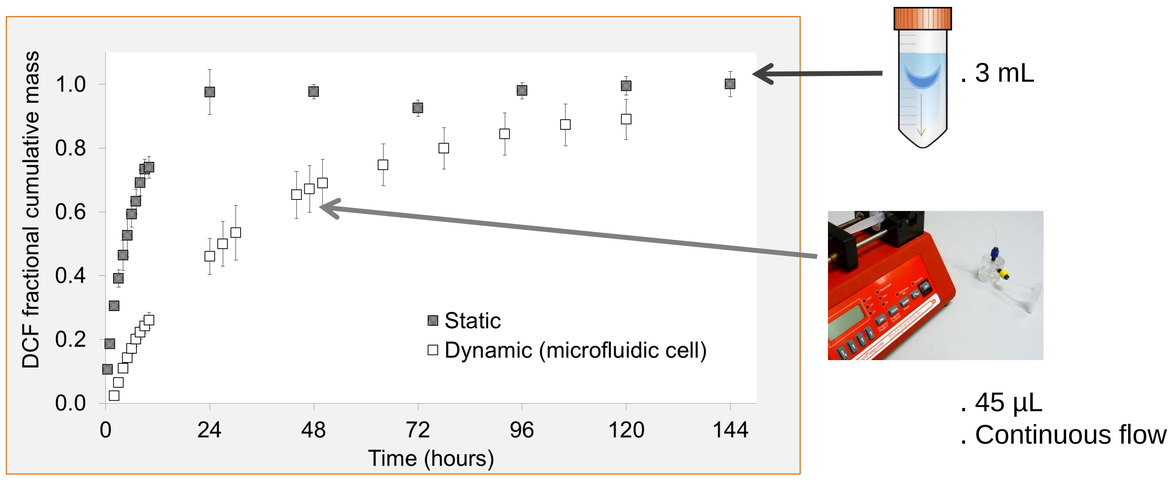


Figure 3. DCF fractional cumulative mass release

⇨ From the release results in dynamic conditions it is possible to estimate the concentration of DCF released from PHEMA hydrogels in a volume equivalent to the tear film.

Considering that….

*The recommend posology for **DCF is 8.5 μg/day** (5 x 1 drop).*

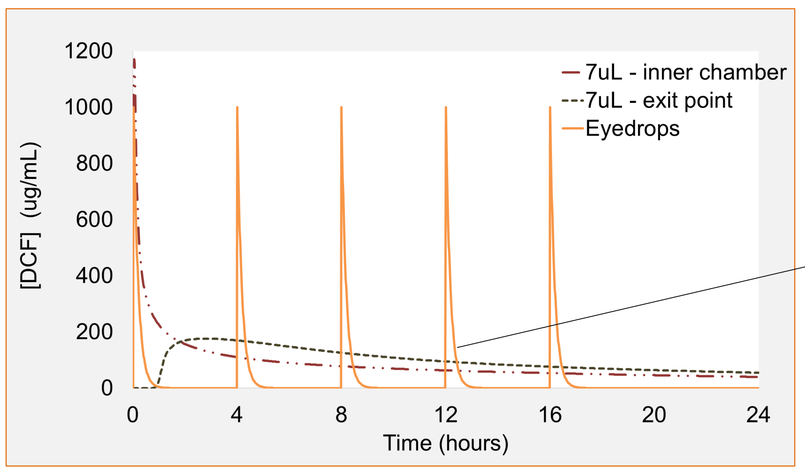


Figure 4. DCF concentration

Table 1. Amount of DCF released from PHEMA , estimated by numerical simulation

Day	DCF mass (μg/lens)
1	420.0
2	127.7
3	54.0
4	22.8
5	9.7
6	3.6

➔ **Results suggest the studied drug/hydrogel pair shall be effective during ≈ 5 days.**

Conclusions

✓ A microfluidic cell was **successfully fabricated** to approximate *in vitro* ocular drug release experiments to the eye tear film *in vivo* hydrodynamic conditions.

✓ Experimental results shown that **DCF release kinetics is affected by the release conditions**; dynamic conditions developed in this study are expected to be closer to the *in vivo* conditions when compared with common sink conditions.

✓ Results suggest the studied **drug/hydrogel pair** shall be **effective during ≈ 5 days.**

[1] Mishima S, Gasset A, Klyce SD, Baum JL, Determination of tear volume and tear flow. Invest Ophthalmol Vis Sci. 1966;5: 264–76.
[2] Robert L. Stamper, Marc F. Lieberman MVD, Becker-Shaffer's Diagnosis and Therapy of the Glaucomas. Elsevier, 8th Edition.