In vitro controlled drug release from contact lenses materials under physiological ocular tear flow

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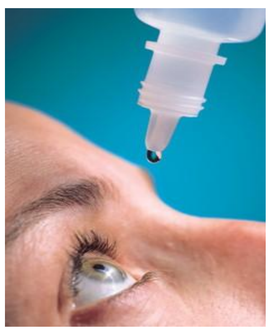
Introduction

Nowadays, over 90% of ophthalmic drugs are administered topically in the form of eye drops [1]. However, the residence time of the drug in the eye is short and only 1% to 7% of the administered drug is absorbed through the eye, leading to poor drug bioavailability and, in some instances, undesirable side effects [2].



In the last few years, efforts have been made to develop more efficient ocular drug delivery systems. Therapeutic soft contact lenses have demonstrated to be an ideal platform for the controlled delivery of numerous drugs as well as comfort molecules [3].

Typically, drug release experiments are conducted under static conditions but, under normal physiological conditions, the human eye presents a reduced tear volume and a tear turnover rate that varies between 1 and 4 µL/min. Thus, to study drug release kinetics in the eye, static conditions do not seem the most appropriate.

Aims

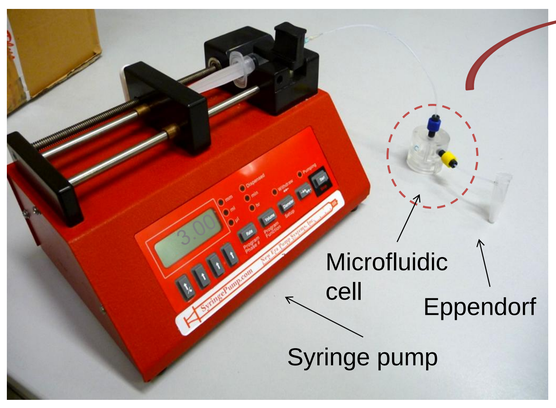
- The present work involves the development of a novel microfluidic cell designed to simulate the physiological conditions found in the eye (temperature, tear volume and flow rate) and therefore more appropriate to test the release of drugs from contact lenses materials.
- Contact lenses were prepared with two types of materials: a hydroxyethylmethacrylate (HEMA) based hydrogel and a silicone based hydrogel. The former hydrogel was loaded with an antibiotic (levofloxacin, LVF) and the latter, with an antiseptic (chlorhexidine, CHX).

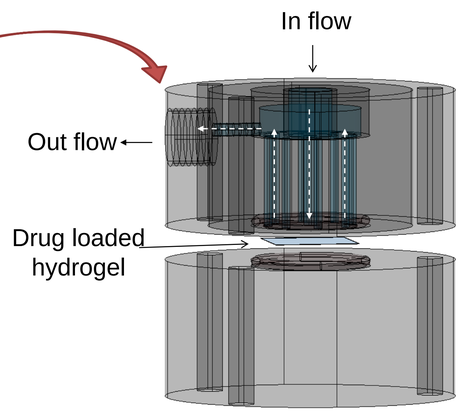
Experimental

- Two different types of hydrogels were prepared by thermal polymerization:

HEMA/PVP (98/2, w/w)	**TRIS/NVP/HEMA (40/40/20 , w/w)**
overnight at 50°C, followed by 24h at 70°C	24h at 60°C

- The hydrogels were loaded by soaking for 14 hours, at 4°C: HEMA/PVP was loaded with LVF (5 and 10 mg/mL solutions) and TRIS/NVP/HEMA with CHX (5 mg/mL solutions).
- The experiments were carried out at 35°C using a microfluidic cell (image below) and in static conditions (2,6mL/lense)

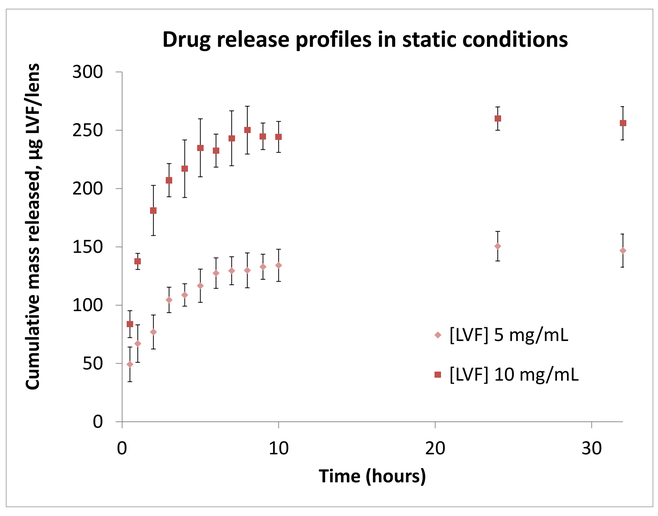


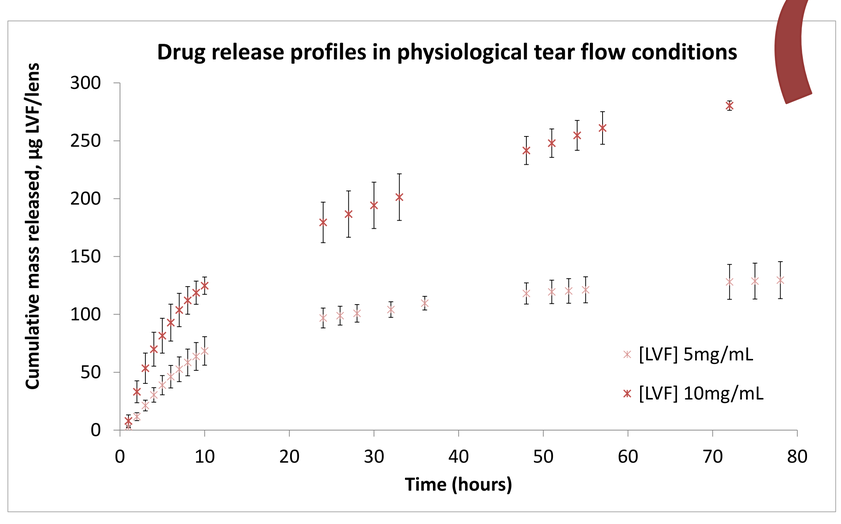


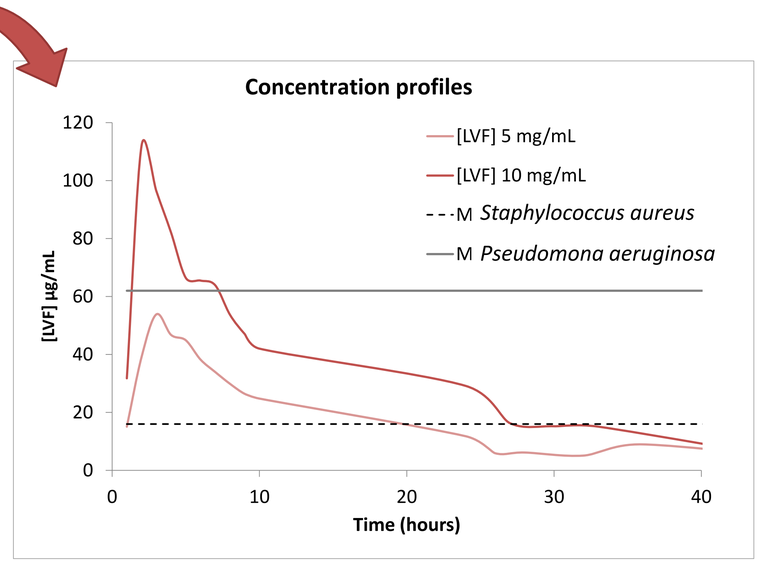
- The microfluidic cell was produced from poly(methyl methacrylate) (PMMA) and engineered to possess an inner chamber in contact with the hydrogel with a volume of 45µL. Isotonic saline solution was allowed to flow directly over the drug loaded hydrogel with a volumetric flow rate of approximately 3µL/min, similar to that of the human eye. Aliquots were collected every hour.
- The drug concentrations of the samples were determined by high performance liquid chromatography (LVF) and by spectrophotometry UV-Vis (CHX).
- The values of the drug concentrations obtained under physiological ocular tear flow were compared with the minimum inhibitory concentrations (MIC) of the antibiotic LVF determined for *S. aureus* and *P. aeruginosa*, and of the antiseptic CHX for *S. aureus*.

Results and Discussion

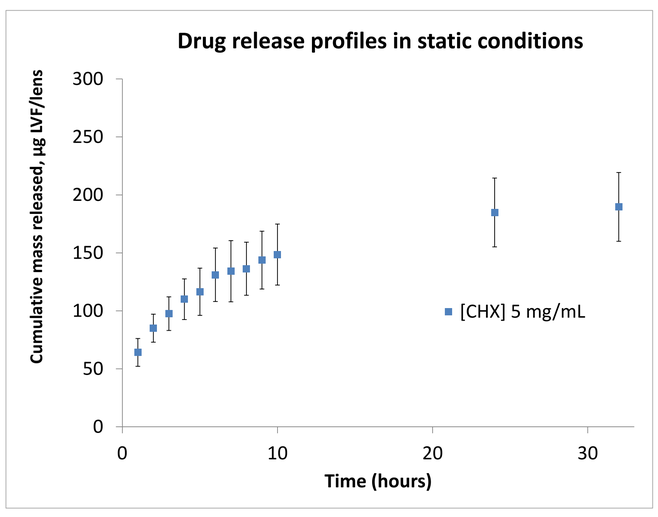
HEMA/PVP, Levofloxacin

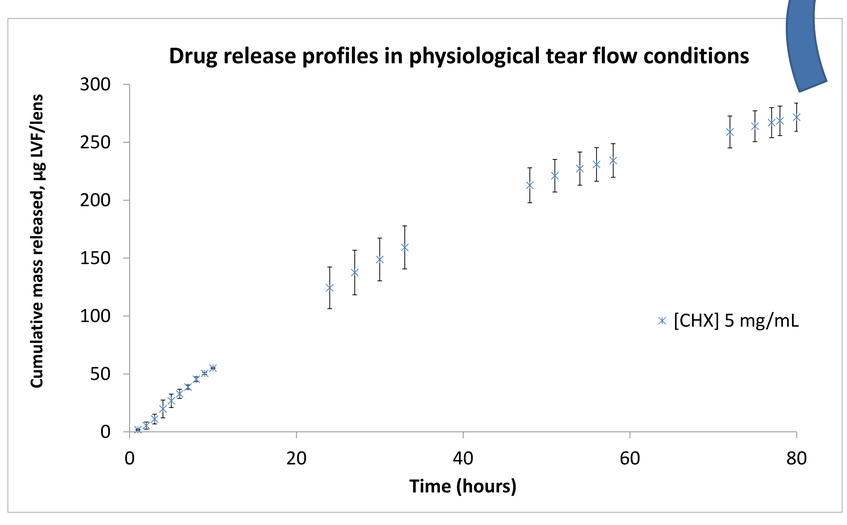


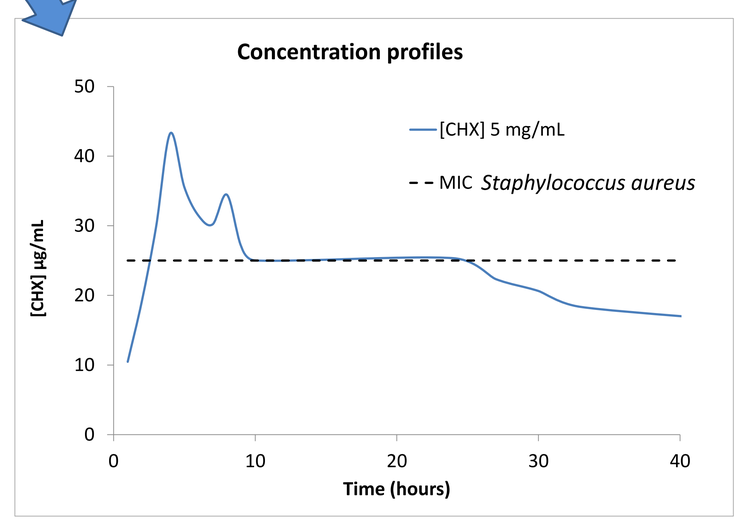




TRIS/NVP/HEMA, Chlorhexidine







- The results obtained under physiological tear flow conditions using the microfluidic cell demonstrate in both cases (HEMA/PVP_LVF and TRIS/NVP/HEMA_CHX) extended drug release for a minimum of 3 days, while the experiments performed in static conditions, showed a maximum release time of 24 hours.
- The comparison of the concentration profiles with the MICs shows that in the case of HEMA/PVP_LVF the concentration of the LVF loading solution had to be increased from 5mg/mL to 10mg/mL, in order to exceed the MIC of *Pseudomona aeruginosa*, while for TRIS/NVP/HEMA_[CHX] 5 mg/mL, therapeutic levels for *Staphylococcus aureus* were maintained along 7-10 hours.

Conclusions

- Results demonstrate that the hydrodynamic conditions significantly affect the drug release kinetics of drugs from therapeutic contact lenses and that extrapolation of results obtained in static conditions to in vivo behaviour should be done with care.
- Both systems seem to be promising for the production of drug loaded daily disposable soft contact lenses.

Bibliography

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