



Ophthalmic drugs and multi dose eyedroppers: a study of container-content interactions in simulated use conditions

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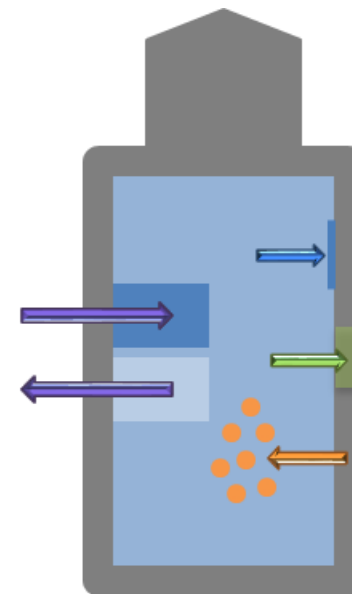
Chef de service du stage d'accueil : Pr Valérie Sautou

Maitre de stage : Dr Philip Chennell

20èmes journées du GERPAC - 4, 5 et 6/10/2017

Introduction

- Context: Preservatives are toxic for the eye⁽¹⁾ => one possibility for the use of preservative-free solutions is multidose eyedroppers containing a sterility preserving device
- Silicone is known to interact with some active substances⁽²⁾
- Objective: Evaluate container-content interactions between silicone and several molecules => Evaluation of active substances in emitted drops
 - Reflection of the real quantity delivered to patient's eyes
 - Clinical setting: concentrations and drop emission rates according to the pharmaceutical use recommendations



Adsorption

Absorption

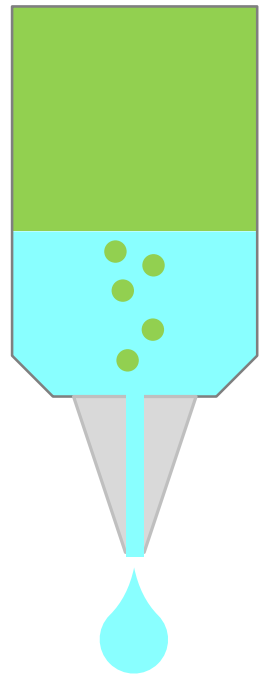
Leaching

Permeation

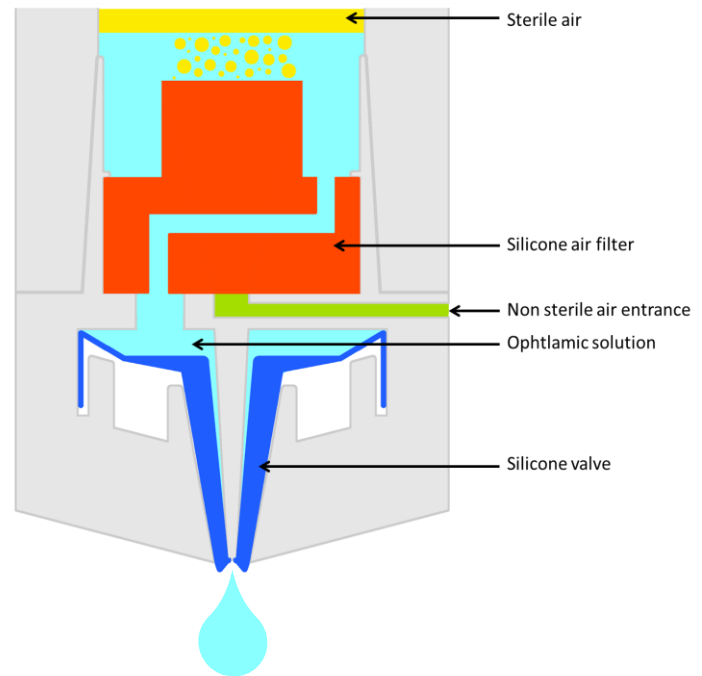
(1): Vaede et al. Les conservateurs des collyres : vers une prise de conscience de leur toxicité. Journal français d'ophtalmologie 2010;33:505-24

(2): Roseman et al. Transport of prostaglandins through silicone rubber. J Pharm Sci 1981;70:562-6

Materials (1) : Eyedroppers

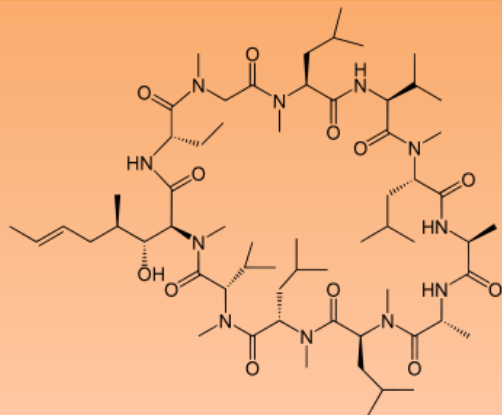


Low Density PolyEthylene (LDPE)

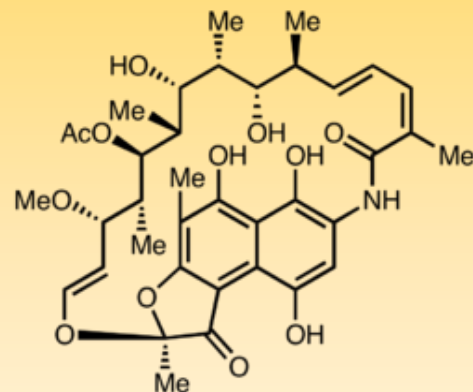


Low Density PolyEthylene with Silicone devices (LDPE-Si)

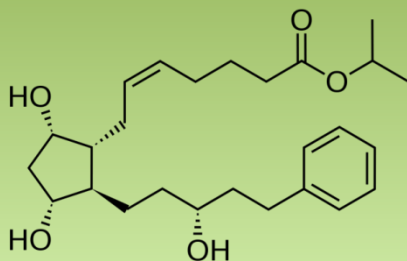
Materials (2) : Tested molecules



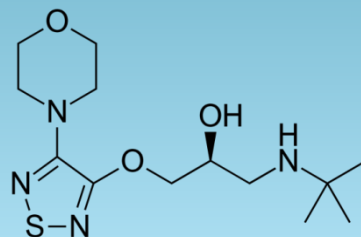
Cyclosporine A
 LogP = 7.5
 MW = 1202.6 g.mol⁻¹



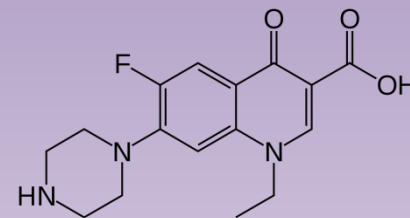
Rifamycin SV
 LogP = 4.9
 MW = 697.8 g.mol⁻¹



Latanoprost
 LogP = 4.3
 MW = 432.6 g.mol⁻¹



Timolol
 LogP = 1.2
 MW = 316.4 g.mol⁻¹

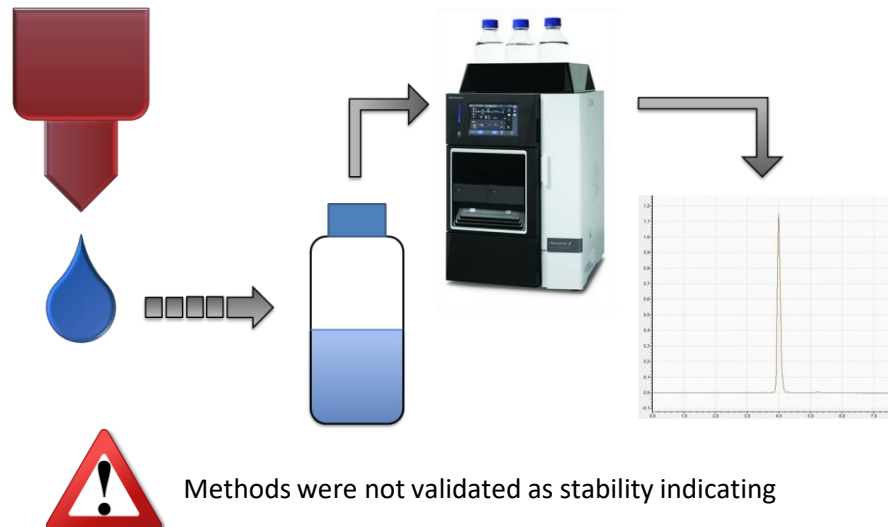


Norfloxacin
 LogP = -1.0
 MW = 319.3 g.mol⁻¹

Methods

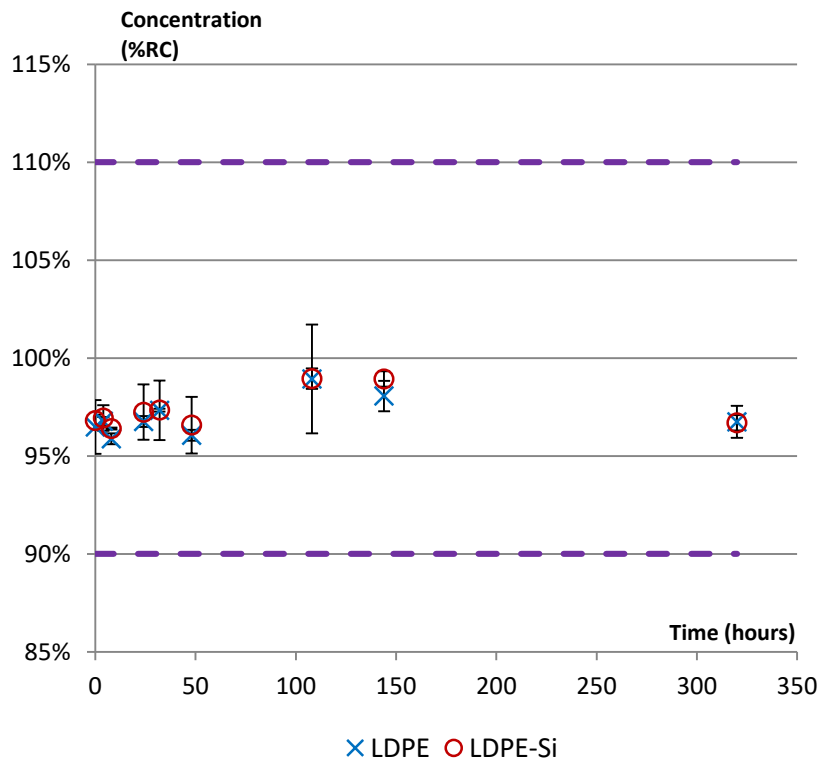
	Conservation	Concentrations studied	Drop emitting rate (/day)	Analyzed drops (drop number)
Cyclosporine A	2-8°C	1, 10 and 20 mg.ml ⁻¹ (0.8, 8.3 and 16.6 mmol.l ⁻¹)	2	1-2-3-5-8-17-28
Rifamycin	25°C	10000 UI.ml ⁻¹ (16.2 mmol.l ⁻¹)	4	1-2-3-5-7-9-14-25-56
Latanoprost	25°C	50 µg.ml ⁻¹ (0.1 mmol.l ⁻¹)	1	1-2-3-5-7-9-14-21-28
Timolol	25°C	2.5 and 5 mg.ml ⁻¹ (5.8 and 11.6 mmol.l ⁻¹)	2	1-2-3-5-8-14-20-28
Norfloxacin	25°C	3 mg.ml ⁻¹ (9.4 mmol.l ⁻¹)	4	1-2-3-5-7-11-19-27-56

- Study was designed to remain within stability limits of the solutions
- Quantification of the initial concentration from eyedroppers of the same batch => reference concentration (RC)
- Quantification of the concentration of residual solution in eyedroppers at the end of drops emission => final concentration (FC)
- Statistical validation
 - Exclusion of aberrant results: Dixon test => $N \geq 3$
 - Significant variation: mean concentration out of a 90-110% range around the RC
 - Difference between eyedroppers: Kruskal-Wallis test



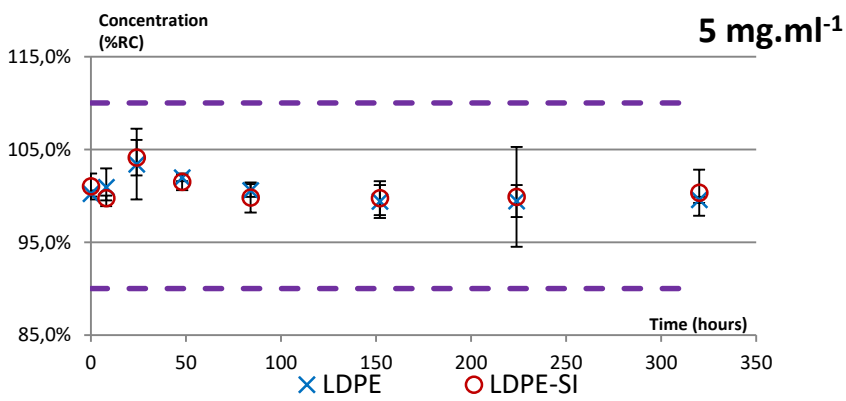
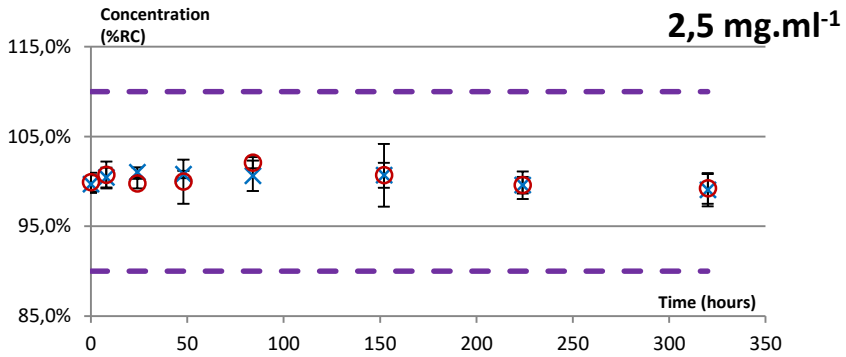
Methods were not validated as stability indicating

Results and Discussion: Norfloxacin



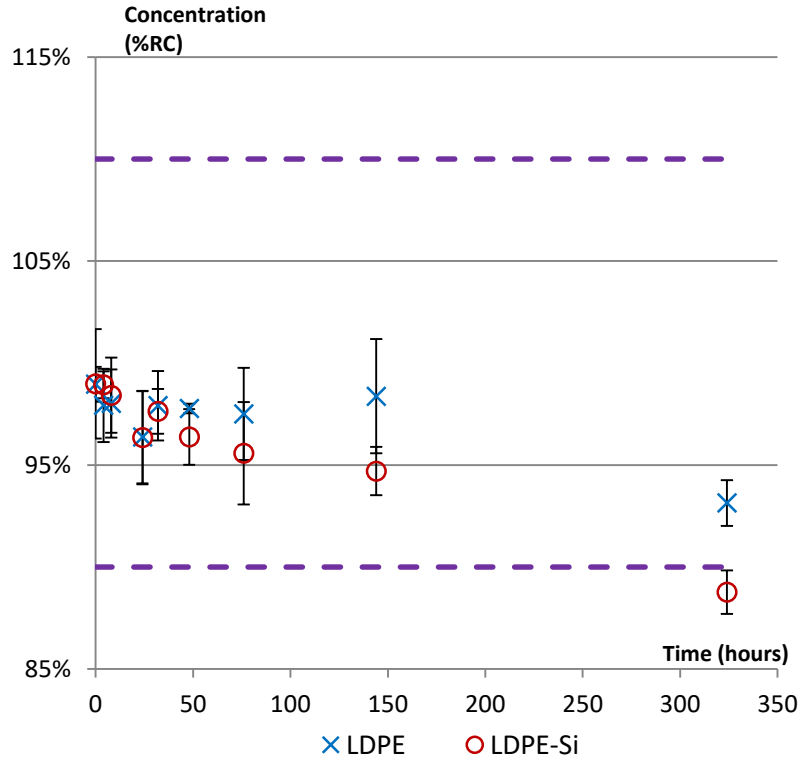
- RC = 3.10 mg.ml⁻¹
- FC_{LDPE-Si} = 3.08 mg.ml⁻¹ (99.8%)
- No significant variation from RC
- No significant difference between LDPE and LDPE-Si eyedroppers

Results and Discussion: Timolol



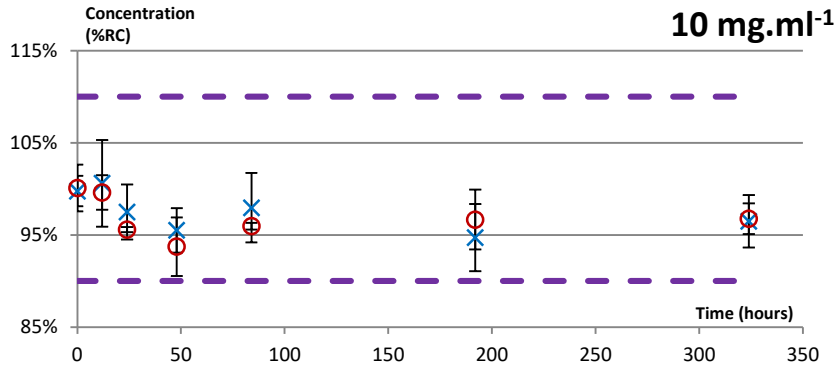
- 2.5 mg.ml⁻¹ eyedroppers :
 - RC = 2.47 mg.ml⁻¹
 - FC_{LDPE-Si} = 2.47 mg.ml⁻¹ (100.1%)
- 5 mg.ml⁻¹ eyedroppers :
 - RC = 4.97 mg.ml⁻¹
 - FC_{LDPE-Si} = 5.00 mg.ml⁻¹ (100.6%)
- No significant variation from RC
- No global significant difference between LDPE and LDPE-Si eyedroppers

Results and Discussion: Rifamycin

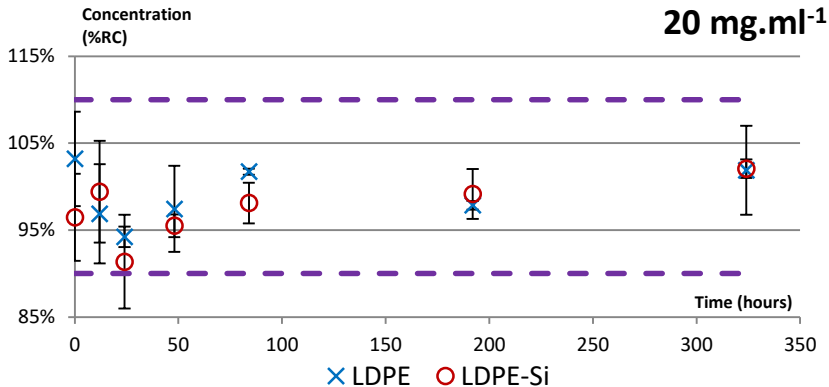


- RC = 10392 UI.ml⁻¹
- FC_{LDPE-Si} = 9274 UI.ml⁻¹ (89.2%)
- No significant difference between LDPE and LDPE-Si eyedroppers
- Significant decrease on the last drop from LDPE-Si eyedroppers
- Interference of degradation ?

Results and Discussion: Cyclosporine A (1)

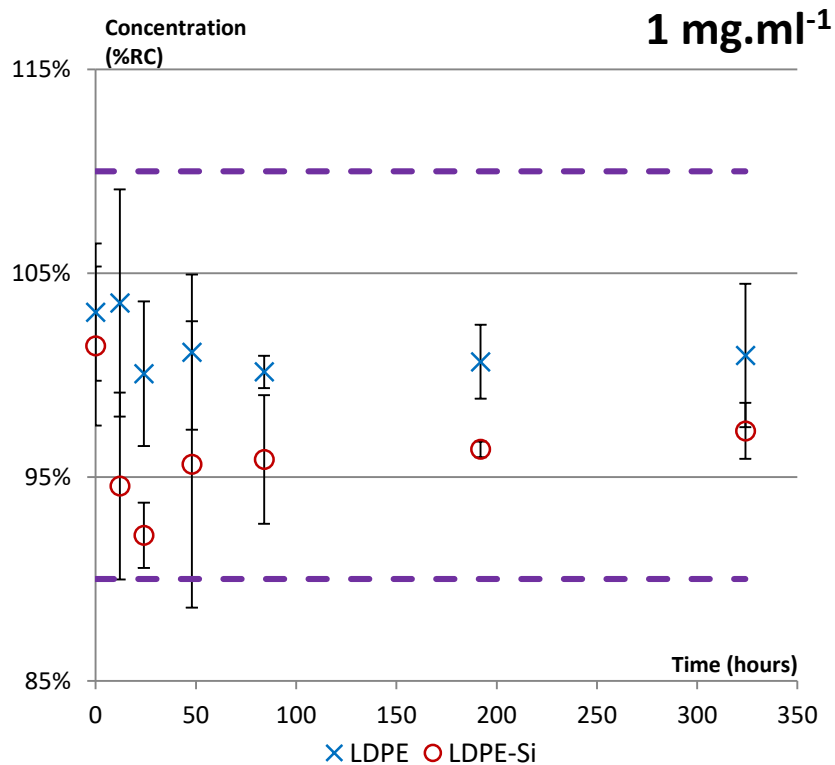


- 10 mg.ml⁻¹ => no significant difference
 - RC = 10.72 mg.ml⁻¹
 - FC_{LDPE-Si} = 10.47 mg.ml⁻¹ (97.6%)



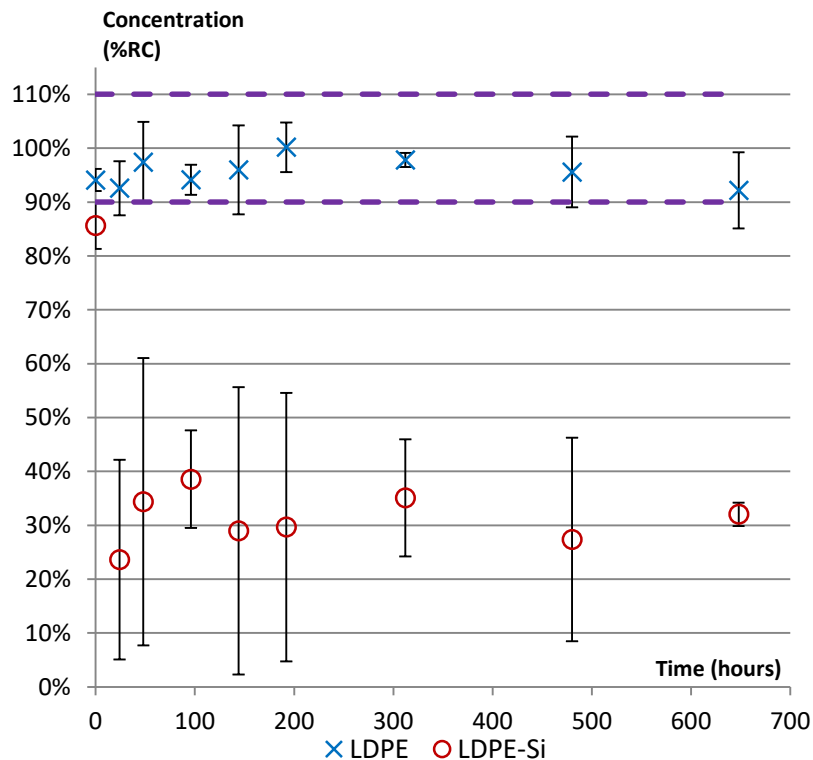
- 20 mg.ml⁻¹ => no significant difference
 - RC = 21.17 mg.ml⁻¹
 - FC_{LDPE-Si} = 19.71 mg.ml⁻¹ (93.1%)

Results and Discussion: Cyclosporine A (2)








- RC = 1.06 mg.ml⁻¹
- FC_{LDPE-Si} = 1.06 mg.ml⁻¹ (100.0%)
- LDPE-Si eyedroppers' concentrations significantly different from LDPE eyedroppers (p = 0.0127)
 - Adsorption (and absorption ?) with no saturation of sites
- No significant variation for LDPE and LDPE-Si eyedroppers

Results and Discussion: Latanoprost



- RC = 50.03 $\mu\text{g.ml}^{-1}$
- $\text{FC}_{\text{LDPE-Si}} = 29.77 \mu\text{g.ml}^{-1}$ (59.5%)
- $\text{FC}_{\text{LDPE}} = 49.81 \mu\text{g.ml}^{-1}$ (99.6%)
- LDPE-Si eyedroppers' concentrations significantly different from LDPE eyedroppers ($p = 0.0003$)
- 76.4% decrease in LDPE-Si 2nd drop, then stabilization around -65% ($15 \mu\text{g.ml}^{-1}$)
- No adsorption in eyedropper's body

Conclusion

				
LDPE eyedroppers		Cyclosporine A Rifamycin Latanoprost Timolol Norfloxacin		
LDPE-Si eyedroppers		Timolol Norfloxacin	Cyclosporine A Rifamycin	Latanoprost

- LDPE-Si eyedroppers = good innovation on the principle and mechanism, but need to be reworked to be adapted to lipophilic active substances

Perspectives

- Further investigations on the different parameters => more fundamental approach
 - pH monitoring
 - Standardization of molar concentrations
 - Responsibility in interactions with silicone => Prediction of the risk of a given solution to undergo a decrease in administered drops concentrations
 - Lipophilicity
 - Molecular mass
 - Drop emission rate (contact time)
 - Formulation
 - Eyedroppers sterilization process
- Supposed impact near expiry date ?

Thank you for your attention !