

Background

Cyclosporine is an immunosuppressive drug known for its narrow therapeutic range (NTR). The only formulation available on the market offers a 100 mg/ml concentration. However, in our hospital, pediatric department regularly requires dosages as low as 4 mg that are difficult to prepare from the pharmaceutical specialty. This may lead to inaccurate doses that can have heavy clinical impact. In this context, we developed a 10 mg/ml cyclosporine formulation.

Purpose

Determine the physico-chemical stability of 10 mg/ml cyclosporine solution in olive oil in order to fix a shelf life.

Material and methods

Solution compounding: 3 batches



- European Pharmacopoeia compliant
- Cyclosporine (FAGRON)
- Olive oil (COOPER)
- Alpha-tocopherol 0,02% v/v (INRESA)

Analytic method validation



- ✓ Linearity: R² estimation, 3 standard curves
- ✓ Accuracy: R%=(C_{meas.}/C_{theo.})x100
- ✓ Repetability: intra-day variability
- ✓ Intermediate precision: inter-day variability
- ✓ Forced degradation by HCl, NaOH and H₂O₂

Analytic method characteristics

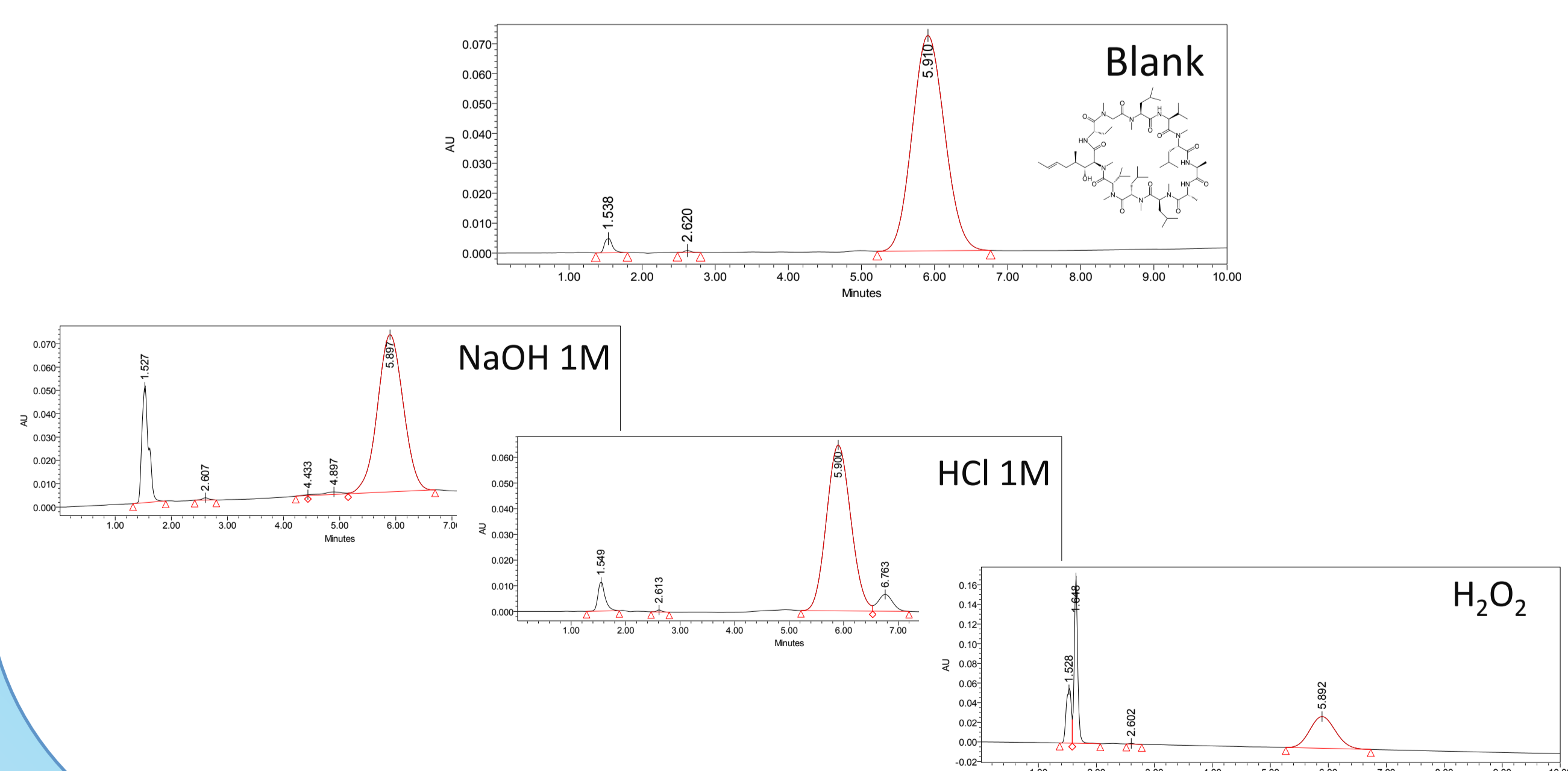


- 717plus autosampler, 2487 UV detector, HPLC 515 pump, Empower® Software
- Column: Waters C18 Xterra (150 x 4,6mm, 5µm)
- Mobile phase: Acetonitrile/Water (70:30 v/v)
- Flow rate: 1ml/min; λ=210nm
- Thermostatic column oven: 60 ± 0,5°C

Days > D0 > D1 > D4 > D10 > D20 > D30

Analytic method validation

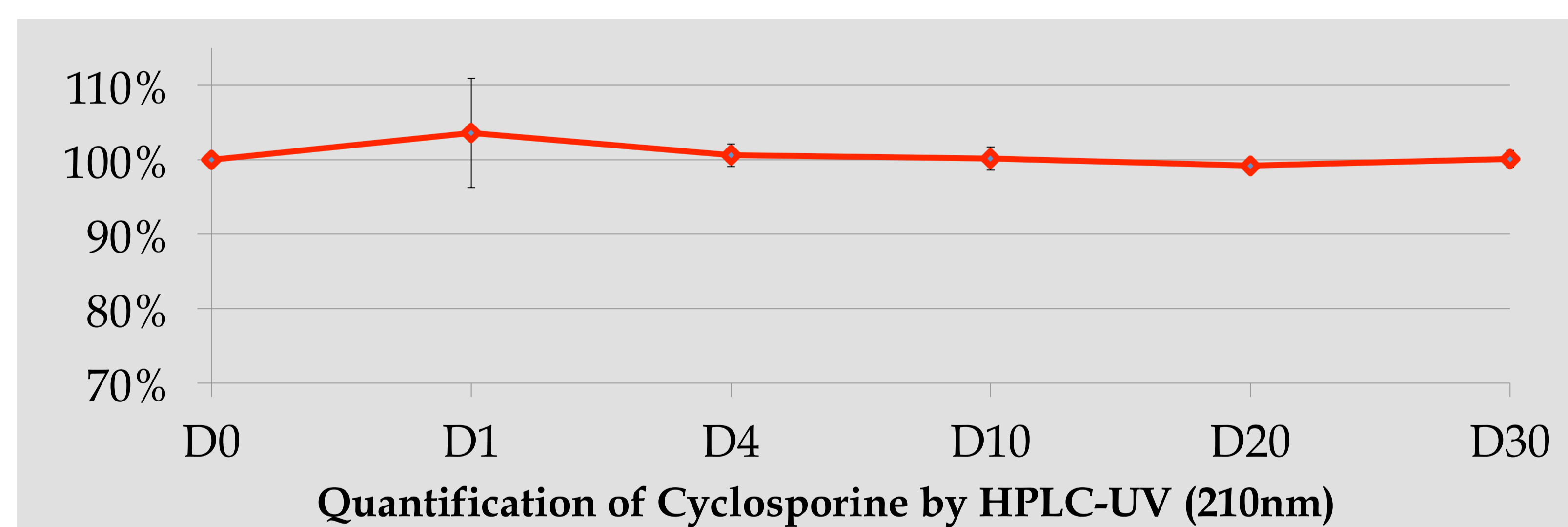
- ✓ No matrix effect was observed
- ✓ Linearity: R²>0,99
- ✓ Accuracy: R%=[99,2%; 98,3%; 99,8%]
- ✓ Repetability: CV=[1,05%; 1,40%; 2,05%]
- ✓ Intermediate precision: CV=1,5%
- ✓ Forced degradation:



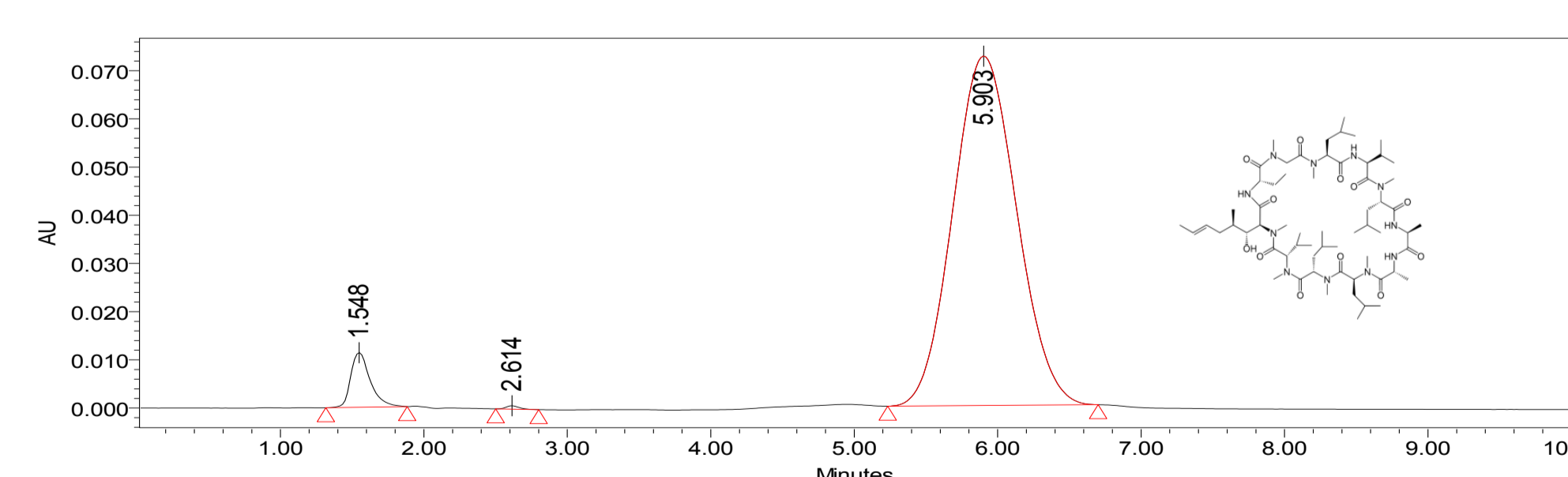
Results

Stability study

- ✓ Cyclosporine concentration evolution over 30 days



- ✓ No macroscopic alteration
- ✓ No degradation products detected



Conclusion

10 mg/mL cyclosporine oral solution in olive oil was stable for at least 30 days at room temperature and protected from light. Therefore we can set a shelf life of 30 days. This 10 mg/ml cyclosporine solution would provide an interesting alternative to the pharmaceutical specialty in order to administrate more accurate cyclosporine doses to pediatric patients.