

# NP – 008 : MIGRATION OF 2,4-DI-TERT-BUTYLPHENOL FROM MULTI-DOSE OPHTHALMIC DEVICES INTO TACROLIMUS PREPARATIONS: INFLUENCE OF FORMULATION

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## Introduction

**SORPTION OF OPHTHALMIC SOLUTION COMPONENT**  
EXCIPIENTS OR ACTIVE INGREDIENT SUCH AS TACROLIMUS (TAC)

**MIGRATION OF OPHTHALMIC DEVICES COMPONENT**  
EXTRACTABLES AND LEACHABLES SUCH AS 2,4 DI-TERT-BUTYLPHENOL (2,4 DTBP)

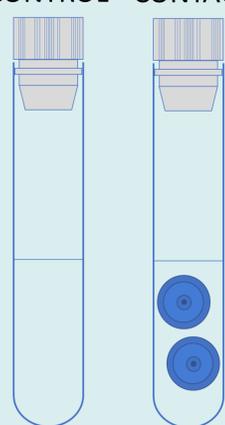
**OBJECTIVE :** Evaluate the impact of different galenic formulation parameters on the leaching of 2,4 DTBP and the sorption of TAC

## Material and methods

**FACTORS STUDIED**

FACTORS STUDIED	SETTINGS
Active ingredient : TAC	0.04, 0.2 and 1 mg/mL
Excipient : Ethanol = EtOH	10 and 100 mg/mL
Excipient : Cremophore® = KEL	32, 80 and 200 mg/mL
Temperature of storage	5 and 25 °C

CONTROL CONTACT



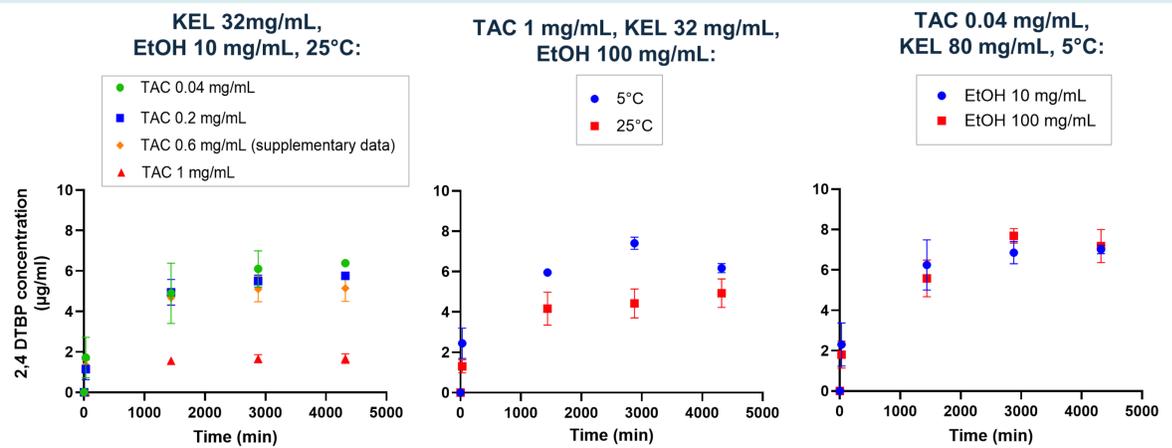
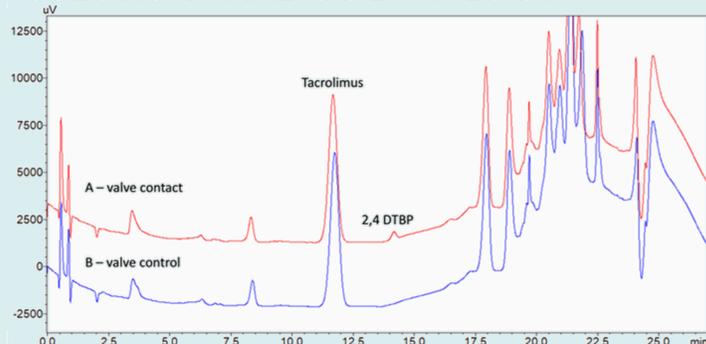
**SOLUTION ANALYSIS BY HPLC-UV**  
QUANTIFICATION OF TAC AND 2,4 DTBP

**MATERIAL SURFACE ANALYSIS**  
X-RAY PHOTOELECTRON SPECTROMETRY (XPS)

Silicone elastomer (**2 valves**) extracted from the ophthalmic multidose device was put into contact with **3 mL** of various tacrolimus (TAC) ophthalmic solutions ( during **3 days**).

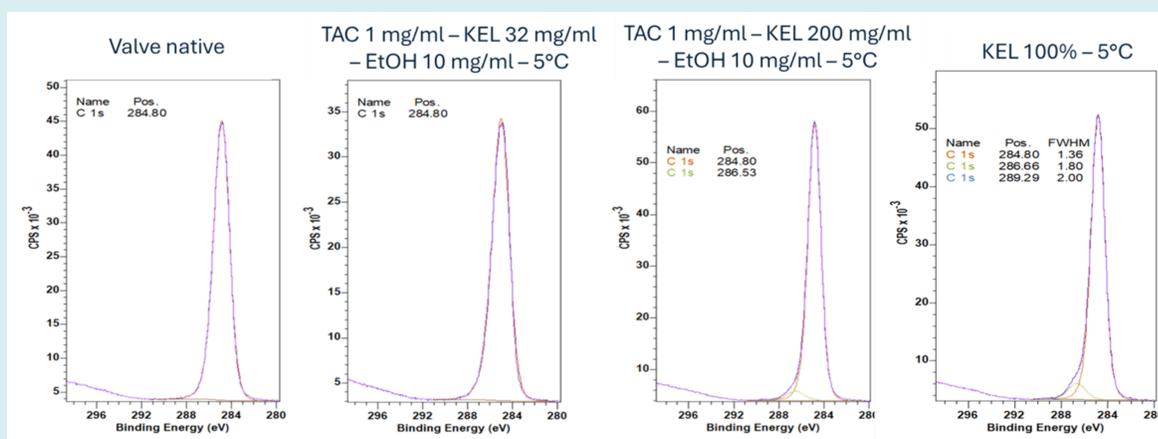
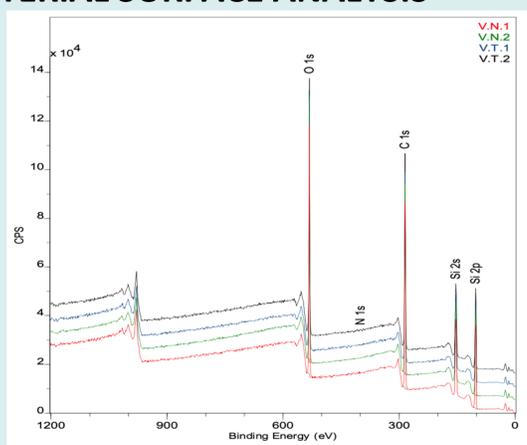
## Results and discussion

### SOLUTION ANALYSIS BY HPLC-UV



**Impact of the formulation :** Under all tested conditions, a leaching of 2,4 DTBP was observed as soon as contact was made with the silicone valves. The leaching of 2,4 DTBP was mainly influenced by TAC : the higher the concentration, the less 2,4 DTBP was extracted. To a lesser degree, the EtOH concentration promoted leaching, while increasing KEL concentration and temperature limited it.

### MATERIAL SURFACE ANALYSIS



**No evidence of TAC sorption:** No nitrogen atoms (characteristic of TAC) visible on the valve surface during XPS analysis: no sorption or not detectable due to there being only one nitrogen atom per tacrolimus molecule ? Surface variations were observed with change in carbon 1s spectra with the appearance of C-O and C=O groups, potentially attributable to the presence of KEL.

## Conclusion

This study highlighted the impact of formulation on the leaching of 2,4 DTBP from silicone valves. The decrease of its extraction in the presence of higher TAC concentrations may be related to the sorption of TAC or KEL on the surface of the valves. In the meantime, manufacturers of delivery devices are encouraged to conduct leachability studies in real-world use situations.

