# Development and validation of a method for the quantitative determination of baclofen and its degradation products for the stability study of experimental medicine.

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## Context and objectives

The Edouard Herriot Hospital pharmacy was solicited to compound 10 mg and 20 mg baclofen capsules for a clinical trial evaluating the efficacy of baclofen versus placebo in reducing the dose of benzodiazepine for patients with benzodiazepine use disorders.

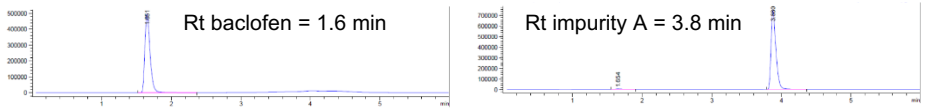
The development of this experimental drug includes the study of its chemical stability using a quantitative analytical method. The specific objective of our study was to develop and validate a quantitative stability-indicating assay for baclofen in 10 and 20 mg capsules by HPLC-MS.

## Material and method

| | | |
|---|---|---|
| *HPLC conditions* | Stationary phase | Octadecyl-silicated 150 x 2,1 mm ; dp = 2.6 µm ; 100 Å |
| | Mobile phase | Solvent A : ammonium formate<br>Solvent B : ACN + 2 % of solvent A |
| | Flow rate<br>Gradient | 0.4 mL/min<br>0 – 1 min : 70 % A - 30 % B<br>1 – 3 min : 70 % A - 30 % B → 30 % A – 70 % B<br>3 – 4 min : 30 % A - 70 % B → 70 % A - 30 % B<br>4 – 7 min : 70 % A - 30 % B |
| | Injection volume - Injection temperature | 5 µL – 20 °C |
| *MS conditions* | Baclofen | m/z = 214 ; tr = 1.6 min<br>LOQ = 0.9 µg/mL – LOD = 0.03 µg/mL |
| | Impurity A (Ph. Eur) | m/z = 196 ; tr = 3.8 min<br>LOQ = 0.12 µg/mL – LOQ = 0.04 µg/mL |
| | ESI Mode<br>$N_2$ Temperature<br>Gas flow rate | Positive mode<br>350 °C<br>12 L/min |
| *Forced Degradation Protocol* | GERPAC protocol :<br>HCl (2 M ; 3 hours) – NaOH (2 M ; 3 hours) – Temperature (60 °C ; 15 days)<br>UV (265 nm ; 6 hours) – $H_2O_2$ (3 % ; 9 days) | |
| *Validation protocol* | GERPAC protocol & SFSTP V2<br>The calibration range was performed within 3 calibration standards: 18, 25 and 32 µg/mL, the validation standards were 20, 25 and 30 µg/mL. | |

## Results

*HPLC/MS conditions*

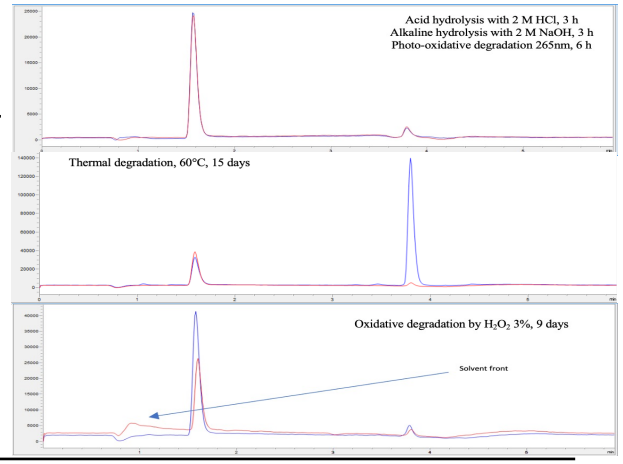



*Forced degradation*

Acidic, alkaline and photo-oxidising conditions :
Did not degrade baclofen, and no impurities and/or degradation products appeared.

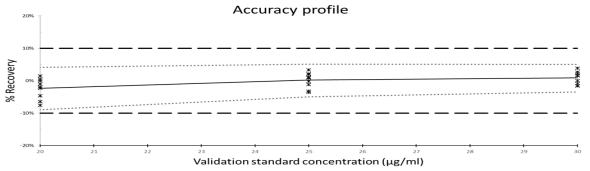
Thermal condition:
Slight degradation of baclofen with impurity A apparition.

Oxidative conditions:
Baclofen was degraded but did not show impurity and/or degradation products.




*Method validation*

Linearity $R^2$ = 0.998 ($R^2$ > 0.99)
Repeatability at 1.48% (CV<5%)
Reproducibility at 2.63% (CV<8%)
Accuracy at 1.13% (CV<10%)




## Conclusion

A quantitative stability-indicating assay by HPLC-DAD-SQ for B-capsules stability assessment was validated. This specific, simple and rapid technique allows us to carry out the stability study of the capsules in this clinical trial