Formulation and physico-chemical stability study of a 5 mg/mL spironolactone suspension: Interest of Capillary Electrophoresis (CE) vs. HPLC

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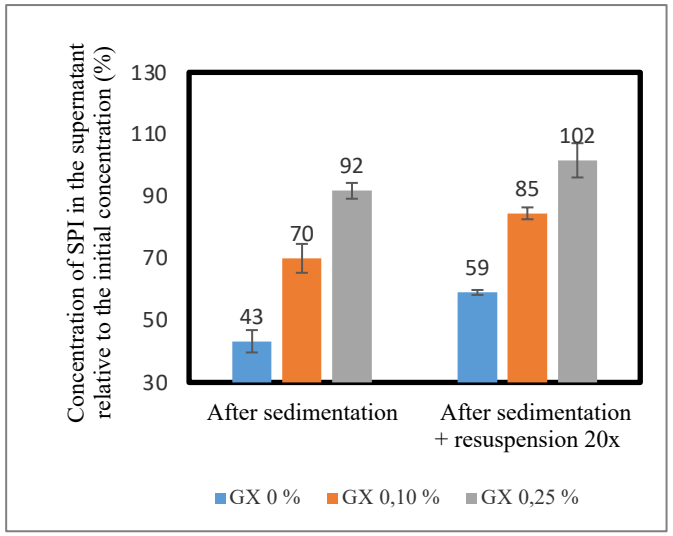
Background: lack of pharmaceutical specialties in doses suitable for paediatric use.
Aim: To develop an oral suspension of spironolactone (SPI) 5 mg/mL and to study its physicochemical stability using capillary electrophoresis (CE) and HPLC.

Formulation: micronised spironolactone in Inorpha® with added xanthan gum.

- Optimisation of the xanthan gum (XG) content by forced sedimentation test: centrifugation at 3000 rpm for 3 minutes.
- 3 XG concentrations: 0%, 0.10% and 0.25%.

Result: Forced sedimentation test



After the forced sedimentation test, 0.25% XG was used to recover 102% of the initial SPI concentration in the supernatant (after resuspension by 20 inversions).

Two assay methods previously validated by the SFSTP (with accuracy profiles):

1. CE

Borate buffer (50 mM, pH 9) + SDS 25 mM/methanol (85/15), voltage at 30 kV, capillary length: 56 cm, injection at 50 mbar for 6 s, detection by DAD.

2. HPLC

Luna phenyl-hexyl column 150 x 4.6 mm x 3 µm, mobile phase: water/acetonitrile/methanol (63/30/7), flow rate set at 1.5 mL/min, detection by DAD.

Development of stability indicating methods.

Identification of peaks by injection of pure substances.

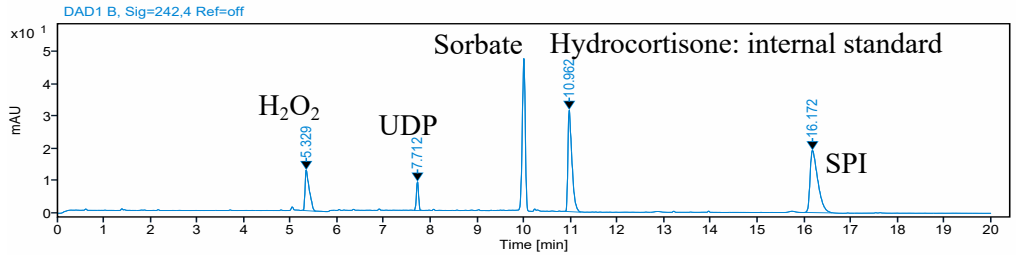
The purity of the peaks obtained was verified.

Result: SPI suspension forced degradation test

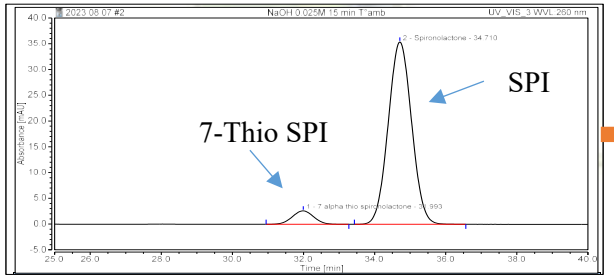
Conditions	Methods	SPI Degradation (%)	Total impurities (%)
NaOH 0,025 M, 15 min-Room temperature	CE	12	9
	HPLC	10	7
HCl 1M, 120 min, 80°C	CE	23	18
	HPLC	7	11
H_2O_2 10 %, 60 min, 80°C	CE	20	20
	HPLC	33	2

NB: λmax SPI: 242 nm, λmax 7-thio-SPI and canrenone (degradation products of SPI): 290 nm, which may explain the differences in mass balance.

CE can identify a degradation product not detected by HPLC under oxidative conditions. However, the detection limit for SPI by CE is 1 µg/mL compared to 0.01 µg/mL by HPLC.

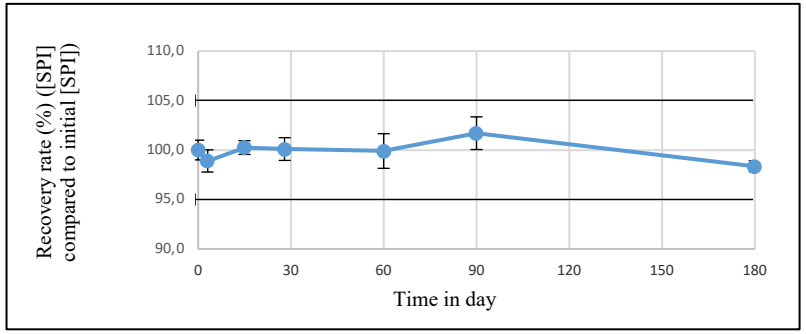


1. CE - Electropherogram at 242 nm. Degradation of SPI suspension in 10% H202 - 80°C, 60 min.
Migration time (MT) SPI = 16.2 min, MT UDP (unidentified degradation product) = 7.7 min.



2. HPLC - chromatogram at 260 nm. Degradation of SPI suspension in 0.025 mM NaOH, room temperature, 15 min.
Retention time (RT) Spi: 35 min, 7-Thio SPI: 32 min.

Results: Stability study: 2 batches over 6 months, in 30 mL bottle, amber coloured [2-8]°C



Conclusion

Physico-chemical stability was demonstrated over a period of 6 months (concentration, absence of degradation products, pH, osmolarity). CE shows all degradation products but with a higher detection limit than HPLC. A microbiological stability study should be performed before validation of the expiration date.