A stability indicating HPLC-UV method for quantification of simvastatin and detection of its impurities in oral capsules

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Background and objectives

A clinical trial sponsored by our hospital wants to compare HMG-CoA reductase inhibitors versus placebo for children with genetic disease. For this purpose, and because the dosage in unavailable, our laboratory is in charge of the formulation development of simvastatin capsule and its placebo. According to Good Manufacturing Practice, the stability of the simvastatin capsule is evaluated, using International Conference of Harmonization Q1C recommendations. Objective is to develop and validate a stability indicating HPLC-UV method for simvastatin capsules.

Method

Sample treatment :
- ✓ Calibration standard are prepared from CRS powder dissolved in a (80:20 v/v) MeOH/H_2O diluent, without matrix.
- ✓ Validation standard are prepared from a 20 mg simvastatine tablet, with matrix (excipients), dissolved in a (80:20 v/v) MeOH/H_2O diluent, after centrifugation.
- ✓ CRS impurities solution prepared as describe in European Pharmacopeia 8.0

Analytical tool :
- ✓ HPLC is a Thermo-Fisher SPECTRASYSTEM
- ✓ Mobile phase is an isocratic buffer with acetic acid 0,1%/MeOH (50:50 v/v)
- ✓ Flow rate is 1 ml/mn
- ✓ Column is an Inertsil CN (4,6 x 250 mm; 5 µm particle)
- ✓ UV detection is included between 200 and 400 nm, with quantification at 237 nm.

Assay validation procedure (according to SFSTP guidelines) :
- ✓ Calibration standard curve is between 30 and 70 µg/ml.
- ✓ Validation standard are 35; 55 and 65 µg/ml
- ✓ Niacine is used as internal standard
- ✓ Linearity, trueness, accuracy, limits of quantification and accuracy profile are evaluated. Matrix effect is assessed.
- ✓ Impurities are searched from SCR impurities of simvastatin dust, according to European Pharmacopeia 8.0

Results

Chromatograms

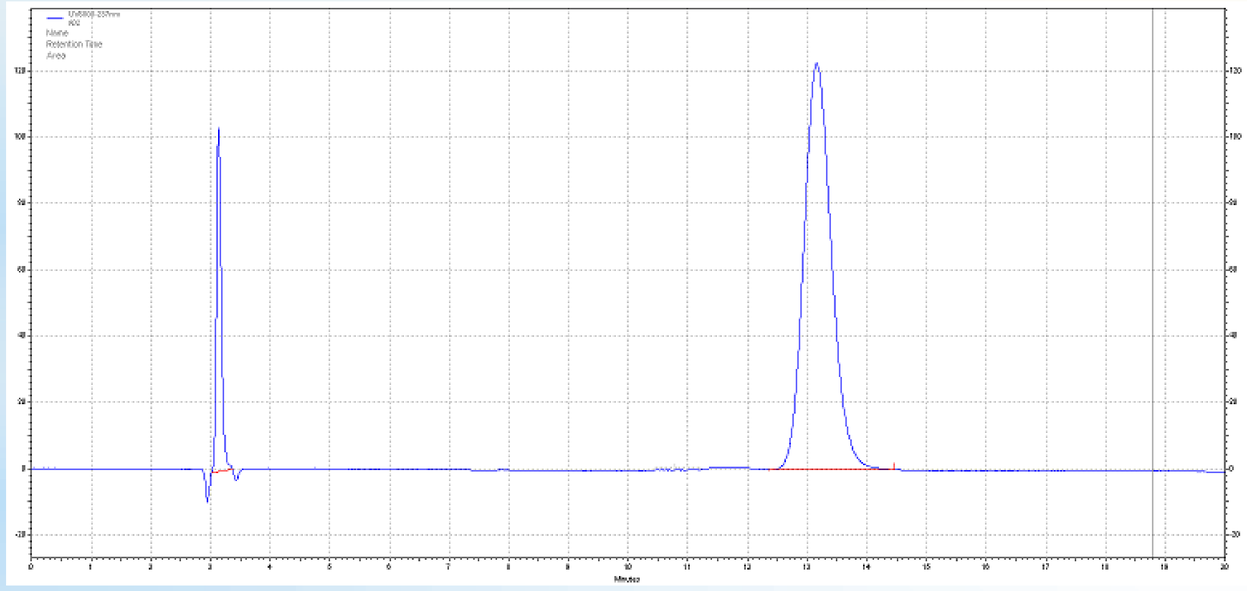

Fig 1 : high calibration standard, tr : 3,25 mn = Niacine; tr : 13,15 mn = Simvastatin

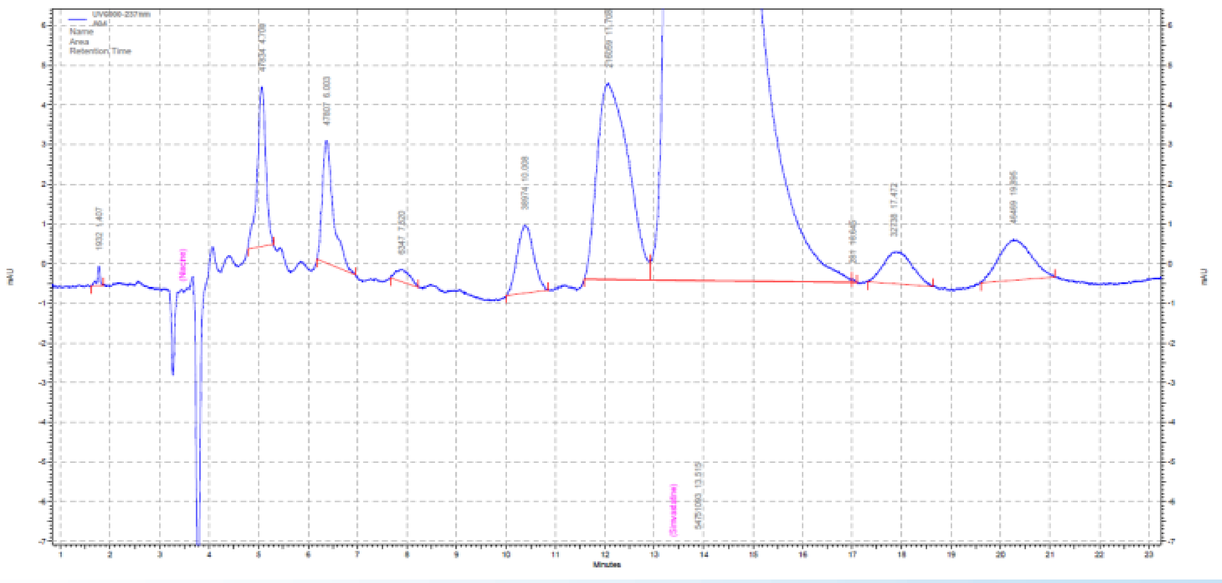

Fig 2 : Simvastatin impurities at 4,7 mn, 6 mn, 10 mn, 11,7 mn, 17,5 mn and 19,9 mn. Rs > 1,5.

Assay validation

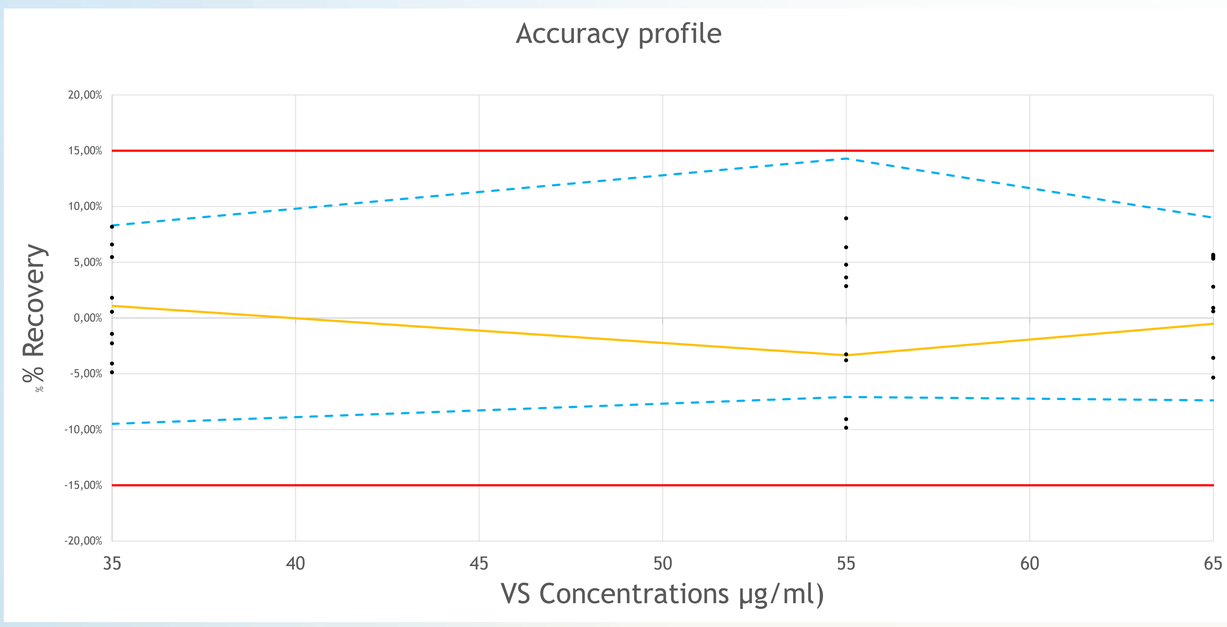

Fig 3 : accuracy profile

Trueness			
	Day 1	***Day 2***	***Day 3***
Biais (%)	1,09%	-3,34%	-0,52%
Recovery (%)	101,09%	96,66%	99,48%

Accuracy			
	VSB	***VSM***	***VSH***
CV intra day (%)	5,34%	6,41%	1,98%
CV inter day (%)	4,46%	5,90%	6,67%

Linearity : calibration curves were linear over the specified concentrations. Biais are < 15 %, R^2 are > 0,99.
Precision and accuracy : coefficient of variation were < 15 % for all the validation standard (ANOVA; R software). Biais were < 15 %.
High and low limits of quantifications were widely outside the range of concentration of the calibration standards. There was ***no matrix effect***.

Conclusion

A simple and rapid stability indicating HPLC-UV method was developed and validated according to ICH and SFSTP international recommendations. It will be used to evaluate the stability of our simvastatin capsule. We already have 6 month of validated stability.

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