Quality control of 5-fluorouracil infusers through packaging

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INTRODUCTION

Analytical quality control of intravenous cancer preparations ensures that patients receive the right drug at the right dose. This control requires sampling. Some types of packaging, as infuser, have no sampling site and cannot be analytically controlled.

The aim of this project was to validate the accuracy of 5-fluorouracil (5FU) dose, non-invasively through packaging, using Raman spectroscopy (RS).

MATERIALS AND METHODS

Spectrometer	i-Raman Prime, 785 nm, 336 mW
Integration time	8000 ms
Focalisation	5 mm
Calibration	5, 10, 15, 20, 50 mg/mL (x3 days)
Validation	8, 18, 40 mg/mL (x3 days, x3 replicate)

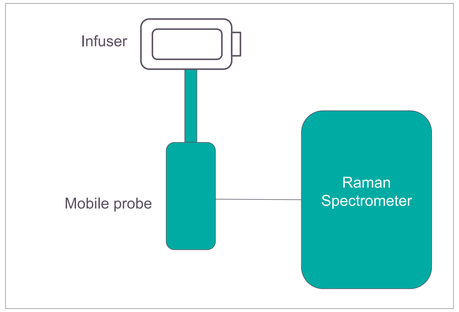

Figure 1. Experimental set-up for measuring vials and infusers by Raman spectrometry.

A 5FU quantification model using partial least squares (PLS) regression over a concentration range from 5 mg/mL to 50 mg/mL through vials was first validated using the accuracy profile method recommended by the Société Française des Sciences et Techniques Pharmaceutiques (SFSTP) with a β interval of 95 % and a limit of acceptance of +/- 15 %

Vial model consutruction	Vial model validation	Infuser bias correction	Routine analysis
Choice of pre-treatments and mathematical model	Estimation of accuracy and fidelity by construction of the accuracy profile	Estimation of bias between vial and infuser measurements based on measurements on standard infusers	In the production area, on patient preparations (n = 9)

RESULTS - DISCUSSION

The spectral region of interest was set between 400 and 2200 cm^{-1}
Pre-treatments were performed on the entire dataset and included
- **Savitzky-Golay smoothing**
- **a weighted least-squares baseline correction**
- **a second derivative.**

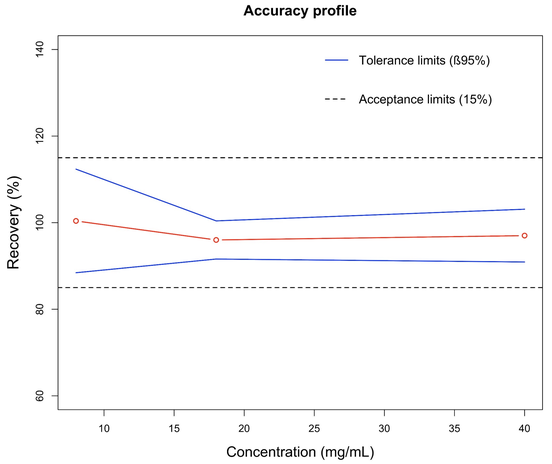

Figure 3. Accuracy profile of 5FU in vials

Analyzing the reference infusers enabled the correction of the predicted results by a part of their multiplicative bias (1.6479, p<0.05)

The mean absolute relative error (MARE) was 8.89% [3.16 - 14.62] IC95.

These results are compatible with the intended routine use of RS for 5FU infusers' quality control.

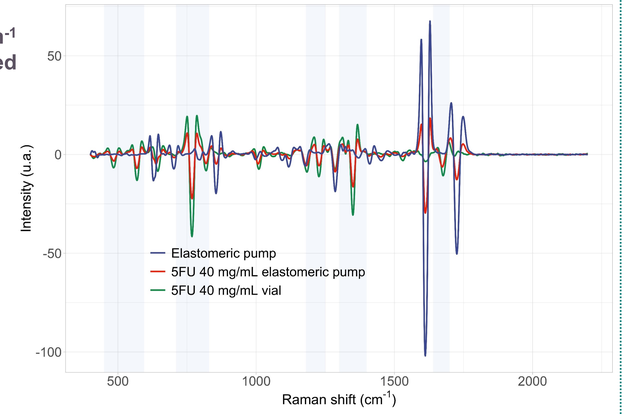

Figure 2. Comparison of pre-treated Raman spectra of 5FU at 40 mg/mL in vials and infusers with the signal from the infuser polymer

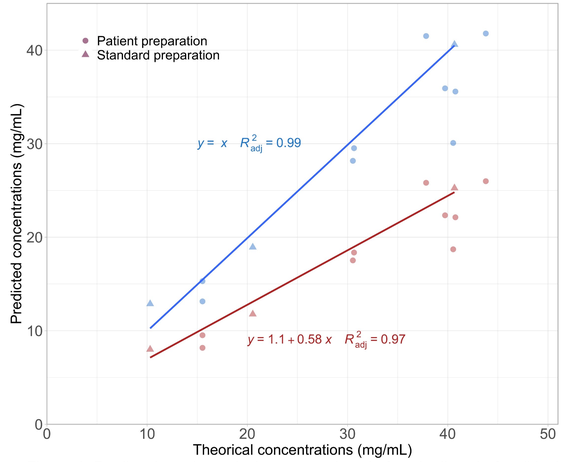

Figure 4. Predicted vs. theoretical concentrations before (red) and after (blue) bias correction

CONCLUSION

The in-vial quantification of 5FU was validated according to SFSTP recommendations over the therapeutic range. The correction of the measurement bias between the vial and the infuser measurement allowed a partial correction of the packaging effect. The feasibility of routine 5FU infuser quantification, through the infuser, has thus been demonstrated. Further tests on patient formulations are currently being performed to confirm the robustness of the method, before applying it routinely to the analytical quality control of hospital-prepared 5FU infusers.

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