Validation of Doxorubicin's calibration ranges using the automatic diluter in Spectroscopy UV-Raman for pre-release dosage formulations of anticancer drugs

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Introduction

The "Unit of reconstitution cytotoxic drugs centralized" (URCC) is a unit which prepares injectable chemotherapy treatments intended for patients with cancer. The URCC has several objectives: to guarantee the quality of microbiological and particulate preparations, to protect staff, the environment and the patient against cytotoxic drugs, to secure the system of anticancer drugs and all within constrained budgets. To reduce medication errors, a quality control tool has been implemented in the URCC: both quantitative and qualitative analytical control preparations pre-release.

Anthracyclines belong to a family of cytotoxic drugs, extracted by bacteria of the genus Streptomyces which presents an anti-tumor activity. The mechanism of action is by inserting of anthracyclines between the two strands of DNA, and causing cell death. However, this mechanism does not only target cancer cells, which explains the occurrence of certain side effects.

The aim of these tests was to measure the parameters such as linearity, accuracy (intermediate precision) for two anthracyclines: Doxorubicin and Epirubicin but here only the doxorubicin will be exposed.

Experimental methods

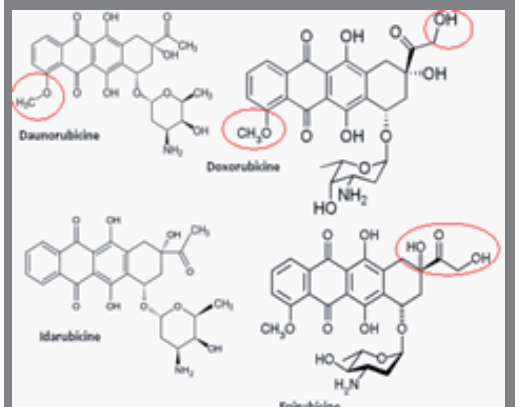
Ranges of calibration were performed on Doxorubicin to validate the automatic diluter and provide the following dilutions: dilution to $^1/_{50}$, $^1/_{20}$, $^1/_{10}$, $^1/_5$, ¼, $^1/_3$, ½, $^1/_{1.3}$ and pure. The dilution operations were conducted for each molecule in two different solvents: NaCl 0.9%and glucose 5% but here only the results of NaCl were used. To validate the diluter, the following parameters were measured: repeatability, accuracy, linearity and intermediate precision. The calibration was repeated over 3 days with 3 points of Quality Control (QC) for 3 different concentrations in each solvent. A total of 54 samples for QC were tested in order to obtain reliable results for the rest of the study.

Results and discussion

Here, only the Doxorubicin in NaCl was examined and results are illustrated in Table 1 and 2. The data of regression generated allows ending in the linearity of the answers in an interval of concentrations included between 0.04 and 2.0 mg/mL. In every case, R2 is higher than 0.999 and the ranges slopes show the pourcentage of deviation (CV) always lower than 5%. All in all, the accuracy of the repeatability of the three QCs, whatever the matrix, the compound, are lower than 10%. The CV of the average QCs obtained during three consecutive days of manipulation compared with the theorical values are lower than 10%.

To conclude, results of tests proved the automatic diluter lead to faithful and accurate results, in both matrices and in the range of the considered concentrations.

Fig.1: Structure of Anthracyclines.



CQ	[ ](mg/mL)	J1 Accuracy (%)	J2 Accuracy (%)	J3 Accuracy (%)
CQ1	0.2	107.00	109.50	108.00
CQ1	0.2	105.00	108.50	106.50
CQ1	0.2	105.50	105.50	106.50
CQ2	1	100.40	101.10	101.60
CQ2	1	99.40	100.80	102.00
CQ2	1	99.90	100.70	101.70
CQ3	2	98.85	99.80	100.80
CQ3	2	100.10	100.10	101.00
CQ3	2	100.05	100.05	101.05

Average	Standard Deviation	CV (%)
0.21	0.003	1.418
1.01	0.009	0.852
2.00	0.014	0.685

Table 1 : An extract of the table of results for Doxorubicin in NaCl: exactitude and intermediaire precision.

Parameters	Securities	Average	SD	CV (%)
a1	16.9963			
a2	16.9750	17.0565	0.1232	0.7222
a3	17.1982			
R^2 1	0.99987			
R^2 2	0.99984	0.99988	$4.04*E^{-5}$	0.00404
R^2 3	0.99992			

Table 2 : An extract of the table of linearity's results for Doxorubicin in NaCl.

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