QUALITY CONTROL OF INFUSIONS IN PATIENT-SPECIFIC PREPARATIONS FOR ONCOLOGICAL TREATMENT

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Motivation

- Within the area of cancer treatment, the therapy regimen is adapted to the patient.
  - Type and dose of the drug are adjusted to the individual needs of the patient.
- Patient individual application solutions are not analyzed.
  - No quality assurance cause a risk of errors.
  - Sources of error: stability-, mixing-problems, underdosing and overdosing, as well as drug counterfeiting and deliberate dilutions.
- Incorrectly dosed preparations can lead to increased side effects or to ineffectiveness.
- To improve quality assurance, we compared chromatography coupled to UV-detection versus a method based on a combined Raman and UV detection system (Raman-UV).

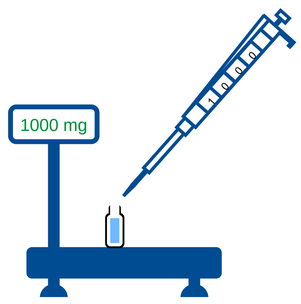
Take home message

- Additional quality assurance can improve the accuracy for patient-specific application solutions.
  - 3.2% incorrect dosages (n=126).
- Advantages of Raman-UV
  - Identification of formulation substances and generics.
  - Good distinguishability of monoclonal antibodies.
- Advantages of HPLC-UV
  - Separation of formulation substances is possible.
  - Robust results with less knowledge about the sample.

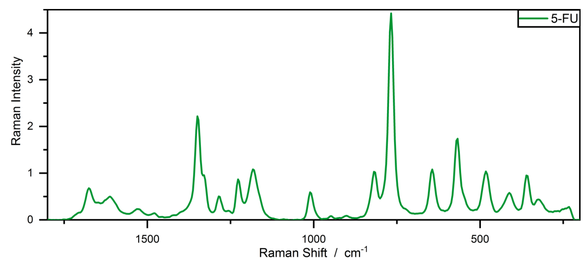
Steps in preparation

1.) Production of patient-specific applications

2.) Gravimetric analysis



3.) Determination of density



4.) HPLC-UV and Raman-UV

Results and discussion

Cytotoxic agents

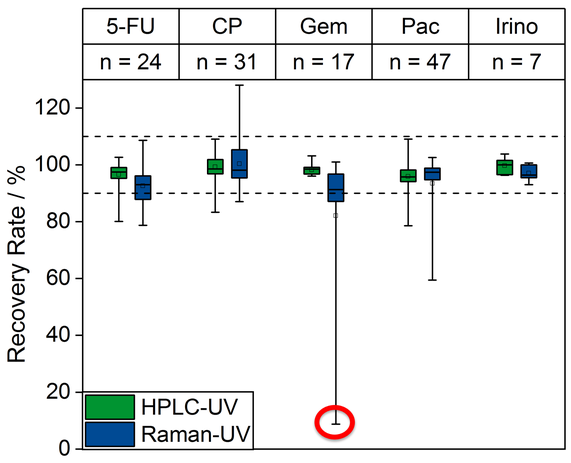


Figure 1: Comparison of recovery rate for the active substances 5-fluorouracil (5-FU), cyclophosphamide (CP), gemcitabine (Gem), paclitaxel (Pac), irinotecan (Irino).

- Analysis of 126 patient specific application bags, measured as triplicate.
- Only the active ingredients were known but not the brand.
- Unknown influences of formulation substances.
- The deviation shall not exceed 10%.
  - HPLC-UV: 4 outlier (3.2%).
  - Raman-UV: 24 outlier (19%).
- The marked sample in figure 1 provides a recovery of 9% compared to 97% by HPLC-UV.
  - Different Raman-Spectra.

Generics

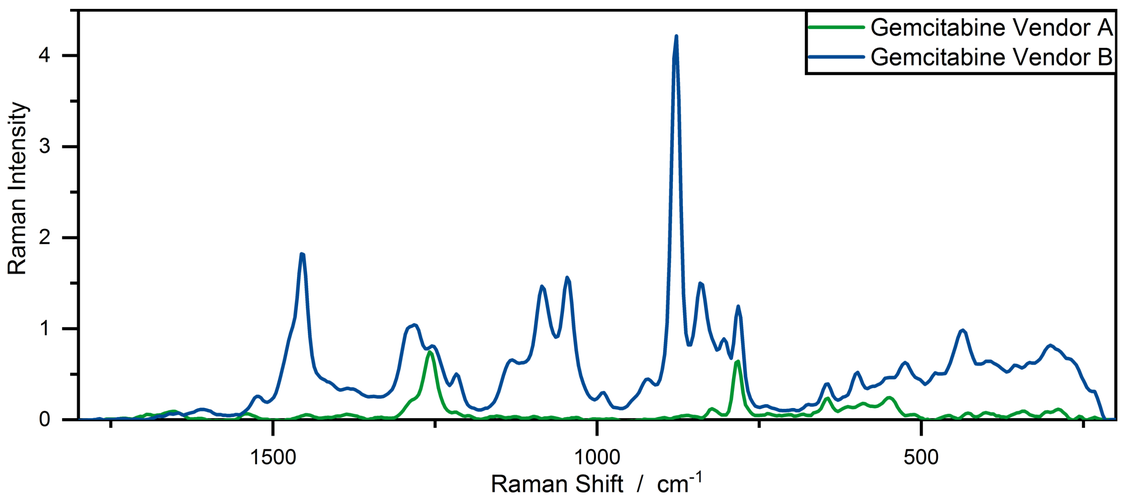


Figure 2: Comparison of the Raman spectra from gemcitabine from vendor B (blue) and gemcitabine from vendor A (green). Gemcitabine from vendor B contains ethanol, polyethylene glycol and propylene glycol as further formulation substances, which are not contained in gemcitabine from vendor A.

- Raman-UV does not separate any formulation substances.
  - Enables the differentiation of generics.
  - Requires a drug specific calibration as demonstrated in figure 2
    - 9% recovery rate using gemcitabine from vendor A calibration.
    - 92% recovery rate using gemcitabine from vendor B calibration.
- HPLC-UV offers the opportunity to separate formulation substances.
  - No drug-specific calibration required.

Monoclonal antibodies

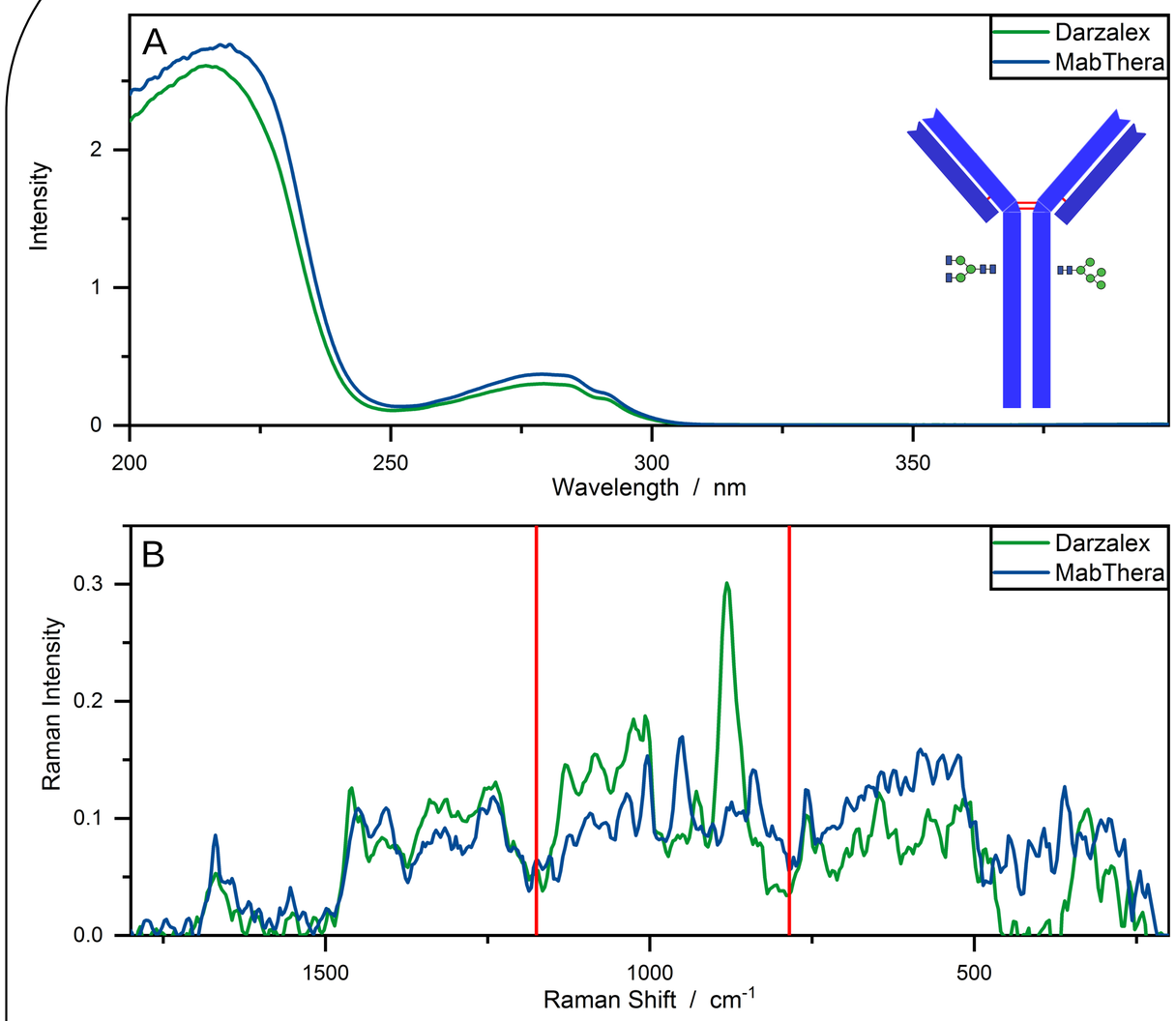


Figure 3: Comparison of daratumumab as Darzalex (green) and rituximab as MabThera (blue) at a concentration level of 4 mg/mL. Figure 3A shows the UV-spectra and Figure 3B the Raman-spectra. The main differences in the Raman spectra are between 1175 cm^{-1} and 785 cm^{-1}.

- HPLC-UV analysis of monoclonal antibodies faces several challenges.
  - Nearly the same UV-spectra (Figure 3A).
  - Difficult to separate with common reversed phase chromatography.
  - Analysis time of several minutes.
  - Very robust quantification is possible.
- Monoclonal antibodies differ significantly in their Raman spectra (Figure 3B).
  - Opportunity of identity testing.
  - Formulation substances can lead to interferences.
  - Quantification via UV, as the Raman signals are very weak.
  - Identification and quantification in approximately 90 seconds.

Acknowledgement

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