Themengebiete Abschlussarbeiten

Stand: Juli 2023
Allgemeines


Interessenten mit konkreten Themenwünschen können sich direkt bei den jeweiligen Doktoranden melden oder allgemein bei Rafaela Meutelet (rafaela.meutelet@kit.edu).
Drug compatibility in adherence technology

**Background**

Development of drug adherence technology is of major importance for efficient medication. To circumvent misapplication, user-friendly handling is inevitable. Self-administration of biopharmaceuticals requires the use of microfluidic devices like micropumps, for instance in patch pumps or pen injectors. However, it is necessary to validate the used micropump for its compatibility with the drug formulations. Of particular interest are the conformational as well as the colloidal stability of the pharmaceutical molecule. Excipients can be added to increase the stability of the molecule during storage and dosing.

**Molecules**
- Monoclonal antibody (mAb),
- Lipid nanoparticle (LNP)

**Projects**
- Process and analytical development for LNPs
  - Microfluidic mixing
  - Tangential-flow filtration
  - PAT
- (Re)Formulation of mAbs
- Stability studies
  - Pump studies
  - Freeze thaw studies

**Analytics**
- HPLC: SEC or RP, Detection: UV/Vis spectroscopy and CAD
- DLS
- Zetapotential
- …
Annabelle Dietrich

Process development, analytical development and PAT implementation for various carrier systems with nucleic acid cargo

Background: Carrier systems with nucleic acid cargo are used for targeted delivery in the field of gene therapy. Specified process and analytical development is of key concern for different carrier systems to ensure their critical quality attributes (CQAs) such as composition, purity, yield, stability and nucleic acid content. CQAs are influenced by critical process parameters (CPPs). Therefore, Process Analytical Technology (PAT) can be applied to monitor process parameters by in-line, on-line or at-line measurements.

Experimental

- **Virus-like particle (VLP)** production by cultivation in *E. coli* and purification by selective precipitation, UF/DF
- **Lipid-nanoparticle (LNP)** production using microfluidics and purification/formulation by UF/DF

Analytics & Tools

- Spectroscopic methods (UV/Vis, Raman, FTIR)
- Light Scattering
- HT-CGE
- HPLC (RP-CAD, SEC-MALS)
- Fluorescence-based assays
- MATLAB

Development

- Yield
- Purity
- Time
- Cost

Carrier → impurities → Purified Carrier

© Tornado
© TECAN
© Malvern
© ThermoFisher
Rafaela Meutelet

Development of an innovative process for the concentration and extraction of nucleic acids for tumour diagnostic (Liquid Biopsy)

Background
Liquid Biopsy provides information about tumours which can help identify disease and guide treatment decisions. It is based on biomarkers found in various body fluids, mostly blood. One of these biomarkers is circulating tumour DNA (ctDNA), short fragments of DNA shed into the bloodstream by cancer cells in very small concentrations. In order to quantify and analyse the mutations of the ctDNA, it needs to be extracted from the plasma and concentrated. The use of Aqueous Two Phase Systems (ATPS) as an initial extraction step is being investigated.

Projects:
- High Throughput Screening of suitable ATPS components and system parameters for optimal DNA partitioning
- Adsorption and desalting step development and integration for further DNA concentration and purification
- Reaction vessel prototype development for integrated extraction of ctDNA from blood plasma

Methods:
- Robotic Liquid Handling Station, automated screenings
- UV/Vis Spectroscopy
- Fluorescence assays
- PCR
- 3D-printing ...

PhD project started 11/2021
Input: The use of **process analytical technologies** (PAT) represents a central aspect of **biopharmaceutical process development**. Spectrometric and chromatographic analysis methods can be used for monitoring and controlling, for example, the purification of pharmaceutically active substances. Both the **optimization of production processes** and the improvement of **process robustness** are in the foreground. In addition, the data obtained can be used to create **mechanistic models**. These models allow the identification of relevant process parameters, the extrapolation beyond the experimental limits, as well as a facilitation of the technology transfer, with a simultaneous **reduction of the number of cost- and time-intensive experiments** necessary for this. Thus, the **improvement of a process** can be achieved under **shortened development time**.

**Materials & Methods**

- **Small-scale model**
  - In-line PAT
  - Process modeling
  - Process digitization

**In lab:**
- Chromatography (Prot.A, AIEX)
- Spectroscopy (UV/Vis, Raman, FTIR)
- Light scattering (MALS, RI, Zetasizer)
- Offline analytics (HPLC-SEC, ELISA)

**Computational:**
- Data management (Python)
- Process-/Analysisautomation (MATLAB)
- Mechanistic modeling (ChromX)
Artificial Intelligence (AI) and Machine Learning (ML) methods provide powerful toolboxes for advanced data analytics with the increasing computation power enabling the use of these algorithms in all sorts of sciences. In bioprocesses, process variables are monitored by in-line or off-line measurements which carry information about the progress of the process. Spectroscopic sensors such as UV/VIS, FTIR or Raman sensors were shown to be reliable sources of process information concerning the concentration of the contained species, excipient concentrations or structural conformations of the components. Parallelly, mechanistic models were established for various unit operations to save experimental time and costs and considerably increase process understanding. AI/ML methods can help to create hybrid modeling strategies where real-time process information is combined with model predictions to successfully implement efficient and precise process control.
Jan Weggen

Advanced methodologies for modelling antibody-drug conjugation

Background: ADC production comprise a set of stirred tank operations, coupled with UF/DF for buffer exchange and at least one chromatographic step. To increase process understanding, enable trouble shooting and ease process characterization as well as scale bridging, a set-up such as a ‘Digital Twin’ is developed.

CFD-based reactor modeling
- Scale-down reactor modeling
- Hydrodynamics-guided process scale-up for ADC reaction
- Full-3D conjugation reaction model

Simulation Methods:
- 0D-Simulations with MATLAB®
- CFD Simulation with Ansys Fluent®

Process modeling and control
- Combining PAT tools with mechanistic models using Kalman Filter
- Bayesian Parameter Estimation
- Modeling of higher DAR conjugation reactions using data-driven models
- Model-predictive control

Experimental Methods:
- Kinetics determination
- Analytics: RP-HPLC, Caliper
- UV-Vis spectroscopy