SUSTAINABLE AND FLEXIBLE PRODUCTION OF HIGH QUALITY CHEMICALS AND PHARMACEUTICALS USING SMART SENSORS AND MODULAR PRODUCTION UNITS

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Safety in Technology and Chemistry
Our Key Areas

BAM is a senior scientific and technical Federal institute with responsibility to Federal Ministry for Economic Affairs and Energy
**Division 1.4: Process Analytical Technology**

**Our Key Areas**

**Gas Analysis**
- Primary Reference Gas Mixtures
- Gas Analysis, Gas Metrology
- Certification of Sec. Gas Mixtures

**Process Spectroscopy**
- Online NMR Spectroscopy, qNMR
- Raman Spectroscopy and Microscopy
- NIR, MIR, FIR spectr., IR Microscopy
- Data Treatment: Statistics, Numerics
- Measurement Uncertainty Evaluation

**Inorganic Process Anal. Technol., XRF**
- X-ray fluorescence Analysis (XRF)
- Laser-induced Breakdown (LIBS)
- Total Reflectance XRF (T-XRF)

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**Process Analytical Technology**

**Motivation**
- optimal design ("quality by design")
- demanded product quality with an optimum use of equipment, raw materials, and energy
- affordable quality costs

**Specification?**
- Feedback
- online-, in-line-, at-line techniques
- physico chemical data
- Non-chemical parameters

**Quality by design**
- objective description of quality
- comprehensive understanding

Located in Berlin, Germany
Innovation and Continual Improvement in Pharmaceutical and Biotechnology Sector

Towards Continuous Pharmaceutical Manufacturing

Conventional Approach

Development and Production

Studies with particular parameter variations

Defined Processes and Specifications (ICH Q6)

“Quality by Testing” (QbT)

Presently Targeted Approach

Quality by Design (QbD)

ICH Guideline Q8 „Design Space”
ICH Guideline Q9 „Quality Risk Management”
ICH Guideline Q10 „Pharmaceutical Quality Systems”
ICH Guideline Q11 „Development and Manufacture”

Process Analytical Technology (PAT)

„Design of Experiments“ (DoE)

Process models on basis of online data

Multivariate data analysis
ICH Q8 „Control Space“ „Real Time Release“ (RTR)

Future Vision

Continuous Manufacturing (CM)

„Real Time Release“ (RTR)

Flexible hook-up of small production facilities

Production transfer

100 % Control

Lack of harmonised approaches for aspects for lifecycle management has hindered the anticipated innovation and continual improvement

Business Plan for a Future ICH Guideline Q12

Future ICH Guideline Q12

More strategic approach to Lifecycle Management (LCM) across the product life cycle

An opportunity to focus on science and risk based approaches for the assessment post-approval changes with the appropriate level of regulatory oversight

Encouraging companies to develop and register more enhanced Quality by Design (QbD) approaches (supporting fuller implementation of Q8, Q9, Q10, and Q11)

Encouraging and providing companies with tools to introduce more innovative approaches to manufacturing

**Online NMR Spectroscopy**

**What is NMR?**

**Nuclear Magnetic Resonance**

1. Dissolve material (and internal standard) in NMR solvent
2. Place NMR tube in magnet
3. Excite sample with RF pulse
4. Record RF signal for several seconds
5. Fourier transform the answer signal
6. Individual molecular segments exhibit highly resolved individual signals
7. Signal areas (integration) are directly proportional to mole fractions

- Molecules stay intact
- See everything in solution (\(^1\)H, \(^{13}\)C, \(^{19}\)F, \(^{31}\)P)
- Direct comparison of mole fractions
- No ionization, no UV
- Detailed information, molecular makeup, structural information, ...
Reaction Monitoring in Lab-scale at BAM

- Syringe pumps
- Reactor setups
- Thermostated transfer tubes
- 500 MHz NMR Spectrometer
- Process NMR
- Process NIR
- Process RAMAN
- Process UV/VIS

Complex reacting multicomponent mixtures
- quantitative information
- qualitative ("chemical") information
- highest possible dispersion

Direct coupling to reactors
- fast and direct sample transfer
- automation
- extended pressure range

Online NMR Spectroscopy
Flow scheme, thermostated bypass

- reservoir
- pump
- split
- NMR
- non-ideal flow: stagnant regions, mixing effects, laminar
- pulse response (RTD)

Tubing:
- PEEK 0.25–0.75 mm ID
- liquid thermostated
Integrated Process Design and Intensified Processes

Current Trend: Hybrid Modular Plants

- Modular Production (Example: Foster Wheeler AG, Zug/CH)
- Micro Reaction Technology (Example: Fraunhofer ICT, Pfinztal/D)

Example: Continuous Flow Production of Pharmaceuticals at MIT

A. Adamo, R. L. Beingessner, M. Behnam et al., On-demand continuous-flow production of pharmaceuticals in a compact, reconfigurable system, Science 352(6281), 2016, 61-67
Process Automation
The Classical Automation Pyramid is Outdated!

- **ERP** = Enterprise Resource Planning
- **MES** = Manufacturing Execution System
- **PLS** = Process Control System
- **APC** = Advanced Process Control
- **SCADA** = Supervisory Control and Data Acquisition
- **PLC** = Programmable Logic Controller

Current and future requirements to process sensors
Sensors go smart

- Smart process sensors are important parts of cyber-physical production systems and generate new business cases for users, instrument manufacturers, and service providers.
- "Smart" sensors provide services within networks and use information out of the network.

- Use of "complicated" sensors has to be simplified towards "plug and play"

"NAMUR Roadmap Prozess-Sensoren 4.0"
From Lousy Interfaces to "Industrie 4.0"
Use of Runtime Environments

Past

sensor → prop. bus → GUI on lab PC → manual data processing → trial and error

Present

sensor → prop. bus → GUI on embedded PC → field bus → runtime environment (PLC) → field bus → process control system
From Lousy Interfaces to “Industrie 4.0”
Use of Runtime Environments


CONSENS

European Union’s Horizon 2020 Research Program
www.consens-spire.eu
Continuous Lithiation Reaction Set-up
Flexible Intensified Continuous Plant

- Fast and complex exothermic reaction
- Hazardous and inflammable substances → Explosion protection!
- Prone to fouling & clogging
- Multi-objective constrained optimization

Example: Lithiation reaction

\[
\begin{align*}
\text{FNB} & \quad \text{Aniline} & \quad \text{Li-HMDS} & \quad \text{NDPA} & \quad \text{HMDS} \\
\begin{array}{c}
\text{NO}_2 \quad \text{NH}_2 \\
\text{F}
\end{array} & \quad \begin{array}{c}
\text{NO}_2 \\
\text{H}
\end{array} & \quad \text{Li} & \quad \begin{array}{c}
\text{H}_3\text{Si} \quad \text{N} \quad \text{Si(CH}_3)_3 \\
\text{Li}
\end{array} & \quad \begin{array}{c}
\text{H} \\
\text{H}_3\text{Si} \quad \text{N} \quad \text{Si(CH}_3)_3 \\
\text{Li}
\end{array}
\end{align*}
\]

Automated NMR-Analyzer Module
Control and Safety Functions

Source: INVITE GmbH
Automated NMR-Analyzer Module
Certification and Documentation

Power supply:
100 – 240 VAC, 10 A circuit breaker

Cooling medium:
1 – 5 °C

Sample feed:
28 °C, 10 bar
(flow cell tested to 50 bar, 100 bar expected)

Nitrogen purge:
6 - 7 bar, min. 140 L/min for purging (~ 2 min)
Leakage rate at 1.9 mbar: 35 L/min

II 2 G Ex pxb db ib IIB T3 Gb

Automated NMR-Analyzer Module
Communication and Data Analysis Concept

Onboard Windows PC
- Automated Matlab analysis
- Spectrometer Software

Programmable Logic Controller
- Data acquisition of sensors
- Triggering of NMR Spectrometer

TCP/MySQL Connection

FailSafe Functions
- Leakage control
- Temperature
- Sample Pressure

Access Point

OPC UA Clients
WAGO Codesys 3
WebVisu

4-20 mA Analog Outputs

NAMUR Status Signals

Conventional World

Industry 4.0 World

Fast Field Bus
Automated NMR-Analyzer Module
Visualization and Control Web Interface (Expert)

09.03.2018 M. Maiwald | BAM | „Using Smart Sensors and Modular Production Units?” | Pfizer Inc., La Jolla, CA; USA

(1) NMR Spectra of Pure Components
Samples of Pure Components (and Mixtures)

Given example: Lithiation reaction, Solvent THF

\[
\begin{align*}
\text{FNB} & \quad \text{Aniline} & \quad \text{Li-HMDS} & \quad \text{NDPA} & \quad \text{HMDS} \\
\begin{array}{c}
\text{NO}_2F \\
\text{NO}_2 \\
\text{N} \\
\text{H}
\end{array} & \quad \begin{array}{c}
\text{NH}_2 \\
\text{H}
\end{array} & \quad \begin{array}{c}
\text{Li} \quad \text{Si} \quad \text{Si(CH}_3)_3 \\
\text{H}_3 \text{Si} \quad \text{Si(CH}_3)_3
\end{array} & \quad \begin{array}{c}
\text{NO}_2 \\
\text{N} \\
\text{H}
\end{array} & \quad \begin{array}{c}
\text{H} \quad \text{Si} \quad \text{Si(CH}_3)_3 \\
\text{H}_3 \text{Si} \quad \text{Si(CH}_3)_3
\end{array}
\end{align*}
\]

- **Low-field NMR spectra**
- **Pure Components**
- **PLS-R** Calibration/validation
- **IHM** Pure Component Model development
Proton NMR Spectra 500 MHz vs 43 MHz
Lab Experiments in Batch Along Reaction Co-ordinate

High field (500 MHz)

Low field (43 MHz)

Data Processing for Low-field NMR in Matlab

- Raw spectra
- Phase correction
- Baseline correction
- Alignment

Single scan each 15s in flow
Data Processing for Low-field NMR in Matlab

**Raw spectra**

**Phase correction**

**Baseline correction**

**Alignment**

**Entropy minimization method:**
Chen et al., *J. Magn Reson.* 2002, 158, 164-168

**Low-order Polynomial fit:**
Data Processing for Low-field NMR in Matlab

Alignment to reference signal (THF) using /coshift:
Savorani et al., J. Magn Reson. 2010, 2, 190-202

Indirect Hard Modeling (IHM)

Modeling peak fitting of pure component spectra → mixture model
Analysis “component fitting” → calculation of component area

- Group of peaks represent pure component spectra
- Pseudo-Voigt function
  \[ V = \alpha \beta \cdot \exp \left( -\ln(2) \frac{(x - \delta)^2}{\gamma^2} \right) + (1 - \beta) \frac{\gamma^2}{(x - \delta)^2 + \gamma^2} \]
  \( \alpha = \) peak maximum
  \( \beta = \) Gaussian-Lorentzian-ratio
  \( \gamma = \) half width
  \( \delta = \) center position

Hard model for pure components
IHM – „Component Fitting“
Interpretation of Experimental Data with Pure Components

Pure component models

Deconvoluted spectrum

Analysis “component fitting”

Position

Height

Width

Experimental spectrum

Modular Exchangeability of Pure Components
(2) Several Lab Experiments in Batch Along Reaction Co-ordinate, Validation with HF-NMR

- IHM = Indirect Hard Modeling; PLS-R = Partial Least Squares Regression

![Diagram of experimental set-up and RTD of high field NMR](image)

(2) IHM: External Validation PLS-R: Model Building From Lab Experiments in Batch along Reaction Co-ordinate

<table>
<thead>
<tr>
<th>Low-field NMR spectra</th>
<th>Pure Components</th>
<th>Batch Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLS-R</td>
<td>Calibration/validation to reference</td>
<td></td>
</tr>
</tbody>
</table>

<table>
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<tbody>
<tr>
<td>Model development</td>
</tr>
<tr>
<td>External validation</td>
</tr>
</tbody>
</table>

![Diagram of NMR spectra and NDPA molecule](image)
(2) Results: Reaction Characterization
Lab Experiments in Batch along Reaction Co-ordinate

3 semi-batch reaction with varying starting concentrations
1500 Spectra for each HF- and NF-NMR

Classification of steady states

Reaction Scheme:

(3) Validation in Tube Reactor
Continuous Lithiation Reaction Lab Set-up at BAM

Step tracer experiments

1/8" tube reactor
(3) Validation in Tube Reactor
Design of Experiments around Process Window

- Independent variation of flowrates / stoichiometric conditions

**Reaction Scheme:**

**Coarse variation:**

**Fine variation:**

Optimal process window

(3) Validation in Tube Reactor
Variation of Set-Points according to Experimental Design

**Low-Field versus High-Field NMR Spectroscopy**

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(3) Validation in Tube Reactor

Variation of Set-Points according to Experimental Design

Low-Field versus High-Field NMR Spectroscopy

<table>
<thead>
<tr>
<th>Toluclid</th>
<th>FNB</th>
<th>Li-Toluidin</th>
<th>Li-MNDPA</th>
</tr>
</thead>
</table>

IHM and PLS-R: External Validation

From Lab Experiments in Batch along Reaction Co-ordinate

Low-field NMR spectra → Pure Components → Batch Reaction → Continuous Reaction

PLS-R
- Calibration/validation to reference
- External validation

IHM
- Model development
- Model parameterisation
- External validation

Already Producing or Still Calibrating?
(4) Validation Runs in Modular Plant
Continuous Lithiation Reaction Set-up at Pilot Plant

Source: INVITE GmbH

Containerized modular plant
Source: INVITE GmbH

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(4) Validation Runs in Modular Plant
Continuous Lithiation Reaction Set-up at Project Partner

Source: INVITE GmbH

June 2017

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(4) Validation Runs in Modular Plant
First Field Tests at Pilot Plant

- Lab Experiments
- PTFE Tube

Validation at Pilot Plant
Ceramics Flow Cell

- Stabilizer Ethylbenzene at 10 wt-% in Li-HMDS reagent
- Modular extension of IHM model from laboratory data successful
(4) Validation Runs in Modular Plant
Final Validation Runs in Pilot Plant

NMR Module
Five Components

Flow Setpoints
iRTO Results
Iterative real-time optimization (iRTO) by Sebastian Engell and Anwesh Reddy Gottu Mukkula
TU Dortmund

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(4) Validation Runs in Modular Plant

Final Validation Runs in Pilot Plant

NMR Module
Five Components

Unwanted oscillations of dosing pump

Wrap-up

Smart Sensors
- Integrated Process Design and Intensified Processes → Current Trend: Hybrid Modular Plants
- Smart process sensors and actuators are important parts of cyber-physical production systems
- Smart field devices generate new business cases for users, instrument manufacturers, and service providers.
- Use of „complicated“ sensors has to be simplified towards „plug and play“
- The classical automation pyramid is not suited for smart field devices

Smart NMR Analyzer Module
- Classical field integration and automation of NMR shown
- Physical Modeling (IHM) enables modular and calibration-free use of NMR → Validation instead of calibration
Outlook

Modular Calibration
- Improvement of Physical Modeling (IHM)
- Derivation from „First Principles“ Methods (i.e., Quantum Mechanics)

„Semantic“ Models

Dissolution Studies by NMR Spectroscopy
Salt Screening and Salt Selection
Multi Component Salts and Polymorphism

API → Crystalline

amorphous → Multi-component

Hydrates → Salts → Solvates → Cocrystals

Polymorphs

mechanochemistry - model systems

Metal organic compounds

Cocrystals

metal ions + ligands → Coordination polymers MOF

API + coformer → cocystal

API + coformer → cocystal polymorphs
In situ - Let's look inside!

Mechanochemistry - LAG
Further Example: Benzamide-Theophylline 1:1
Study of Intrinsic Dissolution Rate by qNMR Spectroscopy

- Varian 500 MHz NMR spectrometer
- Online connection of dissolution vessel close to PhamEur
- \( V = 60 \text{ mL}, \ T = 37 \, ^\circ\text{C}, \ \text{pH 4 buffer}, \ \omega = 100 \, \text{min}^{-1} \)
- Use of ordinary non-deuterated solvents

API compressed into metal ring maintains constant surface

\[ V = 500 \text{ mL} \quad V = 60 \text{ mL} \]
WET Solvent Suppression
Quantitative NMR Results down to 10 ppm API

- No netto magnetisation of solvent signal
- Selective attenuation of solvent signal combined with de-phasing by gradient pulse
- Works quantitatively while omitting transfer of magnetisation to labile protons

WET = water suppression enhanced through $T_1$ Effects

Limit of Detection and Quantification
Example Carbamazepine (according to DIN 32645)

Limit of Detection
Limit of Quantification
Standard deviation of procedure
Critical value of detected signal

$x_{\text{NG}} = 11.7 \text{ mg} / \text{L}$
$x_{\text{EG}} = 23.4 \text{ mg} / \text{L}$
$s_{x_0} = 6.435 \text{ mg} / \text{L}$
$y_k = 0.2488 \text{ a.u.}$
Intrinsic Dissolution Rates

Results for Carbamazepine (CBZ) Pure and Cocrystals

L. Batzdorf et al., Journal of Molecular Structure 1133 (2017) 18–23

Intrinsic Dissolution Rates

Further Example: Paracetamol-Theophyllin 1:1

final concentration of cocrystal = 30 mM

Precipitation effects?

- Paracetamol
- Theophyllin
Liberation Kinetics from Drug Product

Fast Processes need Deconvolution of NMR Signals

Step tracer experiment: e.g., addition of DMSO

NMR response $F(t)$

Convolution

Example: Paracetamol Tablet

Use of Weibull function

$$I = I_0 \left(1 - e^{-\frac{(t-t_0)^b}{a}}\right)$$

Determined Weibull parameters

<table>
<thead>
<tr>
<th>$I_0$ / a.u.</th>
<th>$t_0$ / s</th>
<th>$a$ / -</th>
<th>$b$ / -</th>
</tr>
</thead>
<tbody>
<tr>
<td>$3.44 \cdot 10^{-3}$</td>
<td>7.50</td>
<td>694.32</td>
<td>1.28</td>
</tr>
</tbody>
</table>
Wrap-Up

- Innovation and Continual Improvement in Pharmaceutical and Biotechnology aim at Continuous Pharmaceutical Manufacturing
- Lack of harmonised approaches for aspects for lifecycle management has hindered the anticipated innovation and continual improvement → Q12 (2018)?
- Process Analytical Technology, Integrated Process Design, and Intensified Processes are key technologies

Liberation Studies by qNMR
- Separate observation of API and cocrystal builder is feasible
- Straightforward quantification via internal standard
- Dissolution rate is clearly influenced by cocrystal builder
- Observation of fast processes like, e.g., liberation kinetics possible → using deconvolution

Thank You!

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Anwesh Reddy
Gottu Mukkula TU Dortmund

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