PAT IN FREEZE DRYING:
APPLICATION OF A NEW MASS FLUX MONITOR BASED ON TUNABLE DIODE LASER ABSORPTION SPECTROSCOPY (TDLAS)

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Motivation for Sensor Development: Process Control

- **Freeze drying in general...**
  - expensive and time consuming process.
  - a lot of “science” still unknown.

- **Pharmaceutical freeze-drying...**
  - Use of freeze drying continues to increase with new biotec products.
  - Manufacturing-scale product value in dryer $ / € Millions.
  - Long cycles often made longer by tentative operation ⇒ lack of process monitors.
  - Need to minimize process time for economical and sustainable cycles.
  - Laboratory processes often do not scale to manufacturing due to dryer mass and heat transfer overload.
  - Current monitoring techniques are inadequate in providing measurements of the key operating parameters.

Given the recent emphasis within the FDA on manufacturing science and process analytical technology (PAT), there is an opportunity by applying new modern process monitoring and control concepts to:

- analyse and understand the process
- improve manufacturing efficiency and product quality
Freeze Dryer Process Control - Production Scale

Traditional approach: monitor pressure and temperature

- Batch Method: Control chamber pressure (Capacitance Manometer), 1° drying end point indicated by Pirani + Capacitance Manometer gauges (inexpensive).
- Single vial method: Monitor product temperature
  - Measured via thermocouples in selected vials in 1st row of chamber
  - Problems associated with product temperature monitoring
    - Sterility
    - Freezing bias with sensor: atypical drying behavior
    - Not compatible with automatic loading systems

New technological approaches (examples):

- Manometric Temperature Measurement (MTM) ⇒ measures product temperature at sublimation interface, but limited to pilot scale due to measurement technique.
- NMR ⇒ highly sophisticated method, limited process information (water concentration).

TDLAS: Batch measurement technology, non intrusive optical detection, real-time monitor for the water removal rate & mass balance
**Tunable Diode Laser Absorption Spectroscopy (TDLAS)**

**Definition:**
Tunable Diode Laser Absorption Spectroscopy (TDLAS) is an optical method for detecting trace concentrations of one or more selected gases mixed with other gases.

**Optical measurement of:**

1. **gas (water vapor) concentracion [molecules/ cm^3]**
2. **gas velocity [m/ s]**

   → calculate \( \frac{dm}{dt} [g/ s] \) for product from water vapor concentration & gas velocity data.

   → Integrate the water removal rate during the process to predict the total amount of water removed (mass balance)
Non-intrusive measurement technology, requires only optical access to gas flow

diagnostic duct assembled in Lyostar II (FTS Systems) freeze dryer
**Measurement Principles - Basic Physics**

- **Detector**
- Laser

**vapor flow**

\[ \theta \]

**Normalized Amplitude**

- **Relative Wavenumber \([\text{cm}^{-1}]\)**
- **Normalized Amplitude**

**Graph**

- **Frequency shift** \( \Delta \omega \)
- **Normalized Amplitude**

**Diagram**

**velocity**

\[ u = \frac{\Delta \omega \ c}{\omega_o (\cos \theta_1 - \cos \theta_2)} \quad [\text{cm/s}] \]

Determined using Doppler shift, speed of light, measurement angle and transition frequency

**density**

\[ \rho = \frac{\int \ln(1 / I_o) \ d\omega}{S \ell} \quad [\text{g/cm}^2] \]

Determined using absorption line-strength, pathlength, integrated area and the laser frequency increment

**mass flux**

\[ \frac{dm}{dt} = u \cdot \rho \cdot A \quad [\text{g/s}] \]

Determined using velocity, density and duct cross-sectional area
**Test plan:**
- Conduct a series of four primary drying sublimation tests with water contained in plastic lined bands (bottomless tray + black garbage bags) in the laboratory-scale (FTS Lyostar II) and pilot scale (BOC Lyomax 3) freeze-dryer (full load, ~ 3hrs).
- Execute a 5th complete (1° and 2° drying) product drying cycle of 5% (w/w) mannitol contained in plastic lined bands in each dryer.

**Test conditions, run #:**
- Pure water: run# 1 (0°C, 100mTorr), #2 (20°C, 150mTorr), #3 (40°C, 200mTorr), #4 (40°C, 500mTorr) [100mTorr ~ 0.133mbar]
- 5% Mannitol: run #5 (1° drying: 20°C, 2° drying: 40°C, 150mTorr)

**Specifications (Freeze Dryer & Spool):**

<table>
<thead>
<tr>
<th>Specifications</th>
<th>Lyostar II</th>
<th>Lyomax 3 (round)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modell</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shelf area</td>
<td>0.46 m²</td>
<td>3.34 m²</td>
</tr>
<tr>
<td>Number of shelves</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Condenser capacity</td>
<td>30 kg total</td>
<td>137 kg total</td>
</tr>
<tr>
<td>Spool Length</td>
<td>0.45 m</td>
<td>1 m</td>
</tr>
<tr>
<td>Spool Diameter</td>
<td>8.9 cm</td>
<td>39.9 cm</td>
</tr>
<tr>
<td>Adsorption Pathlenght</td>
<td>13.2 cm</td>
<td>59.5 cm</td>
</tr>
<tr>
<td>Duct Area</td>
<td>62.07 cm²</td>
<td>1237 cm²</td>
</tr>
</tbody>
</table>
Run #1: [H$_2$O] & Velocity Temporal Profiles, Lyostar II

[H$_2$O] and Velocity Temporal Profiles
Run #1 / Lyostar II: (pure water, 3 trays, P$_0$: 100mTorr, T$_S$: 0°C for 1° drying)

- **onset 1° drying:** condenser cooling, start of vacuum pump
- slight increase of c [H$_2$O] indicates onset of loss of pressure control in the drying chamber

100mTorr (at STP) = $3.22 \times 10^{15}$ molecules / cm$^3$

"outgassing" of the chamber = adsorbed water on the shelves and chamber walls
Run #1: Mass Flux Temporal Profile, Lyostar II

Mass Flux Temporal Profile
Run #1 / Lyostar II: (pure water, 3 trays, P_o: 100mTorr, T_s: 0°C for 1° drying)

"outgasing" of the chamber = adsorbed water on the shelves and chamber walls (~ 33.5g)

Sublimation Rate (grams / second)

1° Drying Time (hrs)

ramp rate: 1°C/min

dm/dt calculated by TDLAS

mass flux (gravimetric): 866.4g
mass flux (TDLAS, w/o peak): 842.0g
ratio (grav./TDLAS): 1.03
Run #1: Mass Flux Temporal Profile, Lyomax 3

Mass Flux Temporal Profile
Run #1 / Lyomax 3: (pure water, 3 trays, $P_o$: 133mTorr, $T_s$: 0°C for 1° drying)

Sublimation Rate (grams / second)

1° Drying Time (hrs)

"outgasing" of the chamber
= adsorbed water on the shelves and chamber walls (~120g)

ramp rate: 1°C/min

dm/dt calculated by TDLAS
mass flux (gravimetric): 7.8 kg
mass flux (TDLAS, w/o peak): 7.8 kg
ratio (grav./TDLAS): 1.0
Run #5: Mannitol 5%, Mass Flux Temporal Profile, Lyostar II

Mass Flux Temporal Profile
Mannitol 5% (w/w), P₀: 150mTorr, Tₛ: 20°C (1° drying), Tₛ: 40°C (2° drying)

Sublimation Rate (grams / second) vs 1° + 2° Drying Time (hrs)

- dm/dt TDLAS
- dm/dt calculated by MTM

mass flux (gravimetric): 4298g
mass flux by MTM: 4071g
ratio (grav./MTM): 1.05
mass flux by TDLAS: 4666g
ratio (grav./TDLAS): 0.92

enlargement of mass flux plot: end of 1° drying, 2° drying
Run #5: Mannitol 5%, Mass Flux Temporal Profile, Lyomax 3

Mass Flux Temporal Profile

Run #5 / Lyomax 3: Mannitol 5% (w/w), P₀: 150mTorr, Tₛ: 20°C (1° drying), Tₛ: 40°C (2° drying)

- dm/dt TDLAS
- dm/dt calculated by MTM

Mass flux (gravimetric): 28.53 kg
Mass flux by TDLAS: 28.82 kg
Ratio (grav./TDLAS): 0.99

Enlargement of mass flux plot:
- End of 1° drying, 2° drying

1° + 2° Drying Time (hrs)
## Results - Overview

<table>
<thead>
<tr>
<th>run #</th>
<th>avg. velocity</th>
<th>avg. velocity</th>
<th>avg. mass flux</th>
<th>avg. mass flux</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lyostar II</td>
<td>Lyomax 3</td>
<td>Lyostar II</td>
<td>Lyomax 3</td>
</tr>
<tr>
<td>1</td>
<td>110 m/sec</td>
<td>32 m/sec</td>
<td>0.56 kg hr(^{-1}) m(^2)</td>
<td>0.68 kg hr(^{-1}) m(^2)</td>
</tr>
<tr>
<td>2</td>
<td>108 m/sec</td>
<td>41 m/sec</td>
<td>1.17 kg hr(^{-1}) m(^2)</td>
<td>1.29 kg hr(^{-1}) m(^2)</td>
</tr>
<tr>
<td>3</td>
<td>105 m/sec</td>
<td>79 m/sec</td>
<td>1.31 kg hr(^{-1}) m(^2)</td>
<td>1.55 kg hr(^{-1}) m(^2)</td>
</tr>
<tr>
<td>4</td>
<td>51 m/sec</td>
<td>24 m/sec</td>
<td>1.34 kg hr(^{-1}) m(^2)</td>
<td>2.00 kg hr(^{-1}) m(^2)</td>
</tr>
</tbody>
</table>

### Results Laboratory Scale Freeze Dryer: FTS Lyostar II

- gravimetric
- TDLAS
- $R$ = ratio grav./TDLAS

### Results Pilot Scale Freeze Dryer: BOC Lyomax 3

- gravimetric
- TDLAS
- $R$ = ratio grav./TDLAS

\[
\bar{x} \pm s_d \sqrt{\bar{v}}(x) = 1.02 \pm 0.06
\]

\[
\bar{x} \pm s_d \sqrt{\bar{v}}(x) = 0.95 \pm 0.04
\]
Conclusions

1. Successfully measured water vapor mass flux ([H₂O] and flow velocity) during freeze-drying of water and 5% mannitol in two different freeze-dryers.

2. Measurement sensitivity:

   ⇒ Water vapor concentrations: \( \leq 1 \cdot 10^{14} \) molecules/cm³
   ⇒ Gas flow velocity \( \leq 1 \text{ m/sec to } \geq 100 \text{ meters/sec} \)
   ⇒ Mass Flux determinations \( \leq 0.002 \text{ g/sec to } \geq 2.4 \text{ g/sec} \)

3. Successfully determined 1° and 2° drying endpoints.

4. Comparison of velocity and mass flux pattern in laboratory scale freeze dryer (Lyostar II) and pilot scale freeze dryer (Lyomax 3) revealed no potential restrictions of heat and mass transfer for the pilot scale freeze dryer in case of process scale-up.

Potential applications of TDLAS to freeze drying

⇒ Cycle development (chamber pressure optimization in 1° drying, 2° drying).
⇒ Equipment qualification (sublimation tests).
⇒ Scale-up and transfer from pilot to production.
⇒ Cycle end point detection.