PAT in the Laboratory: Case Studies in the Testing of the SMART Freeze Dryer Technology

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Development of the SMART Freeze Dryer Concept

"Smart" Freeze Dryer: Joint development between UCONN and Purdue through the Center for Pharmaceutical Processing Research (CPPR)

- "Improvement" of MTM equation (1) and development of an "expert system" to optimize a freeze drying process with a single experiment (Charlie Tang)
- Experiments performed on a FTS Durastop freeze dryer

- 2003: Exclusive commercialization license obtained by FTS Systems
- Oct. 2004: Alpha software installed at UConn on Lyostar II freeze-dryer platform
- April 2005: Start of beta-site testing (May '05: Pfizer + Regeneron, Aug. '05: Amgen)
- November 2005: official product release

Experimental setup for Smart beta-site testing developed by UConn; testing period more than 8 months; test included hardware and software
**What is "SMART Freeze Dryer Technology"?**

- Freeze drying process optimization and development by the Freeze Dryer during the first laboratory experiment
- Expert System for Freeze Drying
  - Selection of freezing procedure
  - Choice of target product temperature
  - Selection of optimum chamber pressure
  - Shelf temperature selection in primary and secondary drying
- Feedback from "Manometric Temperature Measurements" (MTM)
  - Isolate chamber from condenser for a short period of time (25 sec)
    - Monitor pressure rise
    - Collect pressure rise data (10 points/sec)
  - Fit pressure model function derived from heat and mass transfer theory (MTM equation) to raw data by non-linear regression analysis
  - Obtain data for the vapor pressure of ice at the sublimation interface \( P_{ice} \) and dry product layer and stopper resistance \( R_p + R_s \)
  - Use fundamental steady state heat and mass transfer equations to calculate parameters, required to delineate and optimize process

### MTM Equation

\[
P(t) = P_{ice} - (P_{ice} - P_0) \cdot \exp \left[ \left( \frac{3.461 \cdot N \cdot A_p}{V \cdot (R_p + R_s)} \right) \cdot t \right] + 0.465 \cdot P_{ice} \cdot \Delta T \cdot \left[ 1 - 0.811 \cdot \exp \left( - \frac{0.114}{L_{ice}} \right) \cdot t \right] + X \cdot t
\]

\[
\Delta T = \frac{24.7 \cdot L_{ice} \cdot (P_{ice} - P_0) / (R_p + R_s) - 0.0102 \cdot L_{ice} \cdot (T_s - T_p)}{1 - 0.0102 \cdot L_{ice}}
\]

**MTM Equation and Use of MTM Data**

Evaluate from steady state heat and mass transfer: temperature of product at sublimation interface (1), rate of sublimation (2), rate of heat transfer and vial heat transfer coefficient (3), thickness of ice layer (4), temperature at the bottom of the vial (5), the appropriate shelf temperature to give target product temperature (6)

\[
T_p = \frac{-6144.96}{\ln(P_{ice}) - 24.01549}
\]

\[
\frac{dQ}{dt} = \Delta H_v \cdot \frac{dn}{dt} = A_p \cdot K_v \cdot (T_s - T_p)
\]

\[
T_s = T_r + \frac{1}{A_p} \cdot \frac{dQ}{dt} \cdot \left( \frac{1}{K_v} + \frac{1}{K_{be}} \right)
\]
Smart Freeze Dryer User Input Screen

SMART Freeze Dryer
Required input parameters

1) Vial characteristics
   - number of (product) vials
   - tubing or molded
   - vial inner surface area

2) Product characteristics
   - Amorphous or crystalline
   - Critical temperature of the product \( (T_g', T_c, T_e) \)

3) Product presentation
   - Fill volume (ml)
   - Fill weight (mg)
   - Concentration (g/g)

Note: most important to precisely determine critical temperature of product (by e.g. DSC or Freeze-Dry Microscopy) ⇒ great impact on cycle design...

Smart Freeze Dryer Testing Procedure

BASIC TEST: verification of procedure and evaluation of basic parameters

- Results obtained with Durastop/MTM comparable to Lyostar/SMART MTM ?
- What is the effective chamber volume of a Lyostar II freeze dryer ? ⇒ input parameter
- Minimum product load (i.e. ice sublimation area) for Lyostar II to obtain valid MTM results ? ⇒ critical for experimental setup

CASE STUDIES: test of SMART performance under a variety of different conditions

- Different product "type" and "critical temperature" settings:
  - one component runs (crystalline): glycine, mannitol
  - one component runs (amorphous): sucrose, trehalose, lactose, maltodextrin, dextran, polyvinylpyrrolidone (PVP), bovine serum albumin (BSA)
  - binary mixtures (i.e. sucrose/BSA) and formulations (Pfizer)

- different vial size:
  ⇒ 5cc, 10cc, 20cc
- different fill volume
  ⇒ \( L_{\text{dry}} \): 0.2 - 1.8 cm
- different load
  ⇒ full / partial load

What is the criteria for a "successful" SMART run ?

1st step – "product quality"
What is the overall appearance of the product (i.e. absence of shrinkage or collapse) ?

2nd step – "optimization success"
MTM product temperature within target ? Close match with thermocouple data ?

Note: testing did not focus on alternative 1st and 2nd drying options
Basic Test: Minimum Product Load for Lyostar II

- A minimum ice sublimation area \( (A_{sub}) \) is necessary to obtain (accurate) product temperature predictions from MTM total time of temperature dominated part.
- A Q-value (part of MTM equation, predicts rate of pressure increase) of 0.2 (or \( A_{sub} = 150 \text{ cm}^2 \)) was reported for a FTS Durastop freeze dryer (52 l; 5% glycine) to maintain MTM temperature deviation from thermocouple within 1°C.\(^3\)
- About 1:1 scale: FTS Lyostar II (107.5 l, 7.5% trehalose). Q: 0.3, \( A_{sub} \): 291 cm\(^2\)

![Graph showing MTM temperature deviation from average thermocouple reading (°C) vs. Q-value [g/L hr Torr]](image)

\[ Q = \frac{3.461 \cdot N \cdot A \cdot T_s}{V \cdot (R_p + R_i)} \]

7.5% (w/w) trehalose:
- 5cc vials \( (A_p: 2.91 \text{ cm}^2) \),
- 1ml fill \( (L_{ice}: 0.37 \text{ cm}) \).

Q values calculated from SMART resistance data.

Case Study I: Primary Drying Cycle Adjustment

<table>
<thead>
<tr>
<th>Product Run #</th>
<th>Smart Input Parameters</th>
<th>Chamber Pressure (mTorr)</th>
<th>Shelf temperature (°C) / Time (min) profile of 1° drying conditions selected by SFD</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% sucrose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Run #1</td>
<td>220 vials, 10cc, 1 ml fill ( A_p: 3.21 \text{ cm}^2, T_s: -34°C )</td>
<td>57</td>
<td>-37.0 / 58 -15.2 / 58 -17.8 / 956 --</td>
</tr>
<tr>
<td>Run #2</td>
<td>220 vials, 10cc, 1 ml fill ( A_p: 3.21 \text{ cm}^2, T_s: -34°C )</td>
<td>57</td>
<td>-37.0 / 58 -13.8 / 58 -15.8 / 60 -17.0 / 840</td>
</tr>
<tr>
<td>5% sucrose</td>
<td>112 vials, 20cc, 3ml fill ( A_p: 5.74 \text{ cm}^2, T_s: -34°C )</td>
<td>57</td>
<td>-37.0 / 57 -24.1 / 57 -21.5 / 1440 --</td>
</tr>
<tr>
<td>5% sucrose</td>
<td>336 vials, 20cc, 3ml fill ( A_p: 5.74 \text{ cm}^2, T_s: -34°C )</td>
<td>57</td>
<td>-37.0 / 57 -18.9 / 177 -23.0 / 897 -14.1 / 471</td>
</tr>
<tr>
<td>7.5% trehalose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Run #1</td>
<td>308 vials, 5cc, 1ml fill ( A_p: 2.91 \text{ cm}^2, T_s: -29°C )</td>
<td>65</td>
<td>-32.0 / 77 -14.2 / 92 -12.1 / 495 --</td>
</tr>
<tr>
<td>Run #2</td>
<td>308 vials, 5cc, 1ml fill ( A_p: 2.91 \text{ cm}^2, T_s: -29°C )</td>
<td>65</td>
<td>-32.0 / 77 -13.8 / 92 -12.1 / 495 --</td>
</tr>
<tr>
<td>6% Pfizer product</td>
<td>161 vials, 10cc, 6.8ml fill ( A_p: 3.89 \text{ cm}^2, T_s: -25°C )</td>
<td>85</td>
<td>-28.3 / 57 -9.4 / 118 22.5 / 238 14.2 / 1316</td>
</tr>
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<td>Run #1</td>
<td>161 vials, 10cc, 6.8ml fill ( A_p: 3.89 \text{ cm}^2, T_s: -25°C )</td>
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</tbody>
</table>

Note: when using "identical" experimental setup \( \Rightarrow \) very good reproducibility of cycle recipe.
**Case Study II: Primary Drying Time**

<table>
<thead>
<tr>
<th>Type of product</th>
<th>Smart Input Parameters</th>
<th>SMART 1° Dry Estimate (hrs)</th>
<th>Endpoint by MTM (± 5 mTorr) (hrs)</th>
<th>Endpoint by Pirani (hrs)</th>
<th>Endpoint by average TC (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% glycine</td>
<td>116 vials, 20cc, 5 ml fill A_p: 5.74 cm², T_c: -30°C</td>
<td>22.9</td>
<td>23.6</td>
<td>22.5</td>
<td>22.7</td>
</tr>
<tr>
<td>10% glycine (annealing step)</td>
<td>112 vials, 20cc, 2 ml fill A_p: 5.74 cm², T_c: -28°C</td>
<td>15.9</td>
<td>13.0</td>
<td>13.6</td>
<td>13.2</td>
</tr>
<tr>
<td>5% lactose</td>
<td>145 vials, 20cc, 3 ml fill A_p: 5.44 cm², T_c: -31°C</td>
<td>16.9</td>
<td>17.3</td>
<td>18.8</td>
<td>18.6</td>
</tr>
<tr>
<td>3% PVP (40kD)</td>
<td>112 vials, 20cc, 5 ml fill A_p: 5.72 cm², T_c: -24°C</td>
<td>20.0</td>
<td>19.0</td>
<td>19.5</td>
<td>18.6</td>
</tr>
<tr>
<td>5% sucrose</td>
<td>112 vials, 20cc, 3 ml fill A_p: 5.64 cm², T_c: -34°C</td>
<td>41.8 (29.9)</td>
<td>27.2</td>
<td>27.1</td>
<td>26.8</td>
</tr>
<tr>
<td>2.5% sucrose</td>
<td>112 vials, 20cc, 3 ml fill A_p: 5.64 cm², T_c: -36°C</td>
<td>41.2 (20.1)</td>
<td>20.5</td>
<td>20.3</td>
<td>20.0</td>
</tr>
<tr>
<td>5% sucrose + 5% BSA</td>
<td>178 vials, 10cc, 5 ml fill A_p: 3.58 cm², T_c: -23°C</td>
<td>28.5</td>
<td>54.6</td>
<td>53.5</td>
<td>27.9</td>
</tr>
</tbody>
</table>

- Good agreement in primary endpoint detection by Pirani, TC and MTM.
- SMART estimate of 1° drying shows mixed results:
  - some cases where 1° dry estimate too long, steady state ?
  - one case where estimate is far too short, why ?

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**Case Study II: Primary Drying Time**

- **1° dry endpoint by avg. TC**
  - most of the ice is removed after ~ 30 hrs (agreement with TCs).
  - still removal of water in the final phase ⇒ P_{ice} still high.
  - agreement between MTM and Pirani at the end of primary drying.
Case Study III: Product Resistance

- Reproducibility of product resistance ($R_p$) is important to confirm structure consistency of the product during various cycles (using identical cycle conditions).
- Moreover, $R_p$ may provide important information about freezing (supercooling, nucleation) and/or primary drying behavior (e.g., shrinkage, collapse).
- For classes of $R_p$ dependency of dry layer thickness ($l$) have been reported can be expressed by a simple "one parameter" measure of the entire resistance vs. thickness curve: [4]

$$\hat{R}_p = R_p(0) + \frac{A_1 \cdot l}{1 + A_2 \cdot l}$$

$l =$ dry layer thickness

$R_p(0) =$ resistance at $l = 0$

$A_1, A_2 =$ constants

Sucrose formulations show very good reproducibility in product resistance for varying fill depths. As the dry layer thickness increases, the resistance increases according to model behavior.

Deviation for high fill depth due to heterogeneity in freezing behavior?

20% sucrose shows significant higher $R_p$ values than found for 5%.
Case Study III: Product Resistance

Example: $R_p$ data provide valuable information about product "behavior":
- 5% PVP: decrease of $R_p$ after about 50% of primary drying
  ⇒ microcollapse? cracks in the cake?
- 10% lactose run shows higher $R_p$ values at the beginning of cycle
  ⇒ high resistance amorphous skin?

Case Study IV: Product Temperature by MTM

- Product temperature at the sublimation interface ($T_p$) does not exceed the critical product temperature during ice sublimation.
- $T_p$ by MTM provides interface temperature which can be lower than the temperature at the bottom center (temperature gradient).
- The temperature at the bottom of the vial ($T_b$) is calculated by SMART software based on an assumption that all heat ($dQ/dt$, cal/h per vial) provided by the shelf is consumed by ice sublimation:

$$T_b = \frac{(dQ / dt) L_{ice}}{A_1 K_{ice}} + T_p$$

- MTM predicts a temperature which is representative for the vials which are running on the coldest product temperature in an arrangement of vials [3]
  ⇒ use temperature measured with a thermocouple in the "center bottom" of a vial in the center of a batch as a reasonable comparison...
  ⇒ difficulty: accurate placement of thermocouples...

\[dQ/dt; Heat \ Flow \ calculated \ by \ MTM \ (cal/hr/vial)\]
\[L_{ice}; calculated \ ice \ thickness \ (cm)\]
\[A_1; area \ of \ outer \ vial \ bottom \ (cm^2)\]
\[K_{ice}; thermal \ conductivity \ of \ ice \ (20.52 \ cal/hr \ cm^2 K)\]
\[T_p; product \ interface \ temperature \ from \ MTM\]
Case Study IV: Product Temperature by MTM

- With typical excipients and concentrations used in freeze drying, very good agreement until about 50% of primary drying was found for thermocouple and MTM ($T_b$) product temperature data.
- Be careful to restrict "accuracy" of this temperature comparison (a few vials vs. avg. batch) to a "full match" between data sets during your routine work.

![Graph 1](image)

Case Study IV: Product Temperature by MTM

- Atypical results were found with concentrations higher than 3% of PVP.
- Initial data analysis showed that "error" may arise from $P_{icer}$ not $R_p$ ⇒ theory of a "water re-adsorption" effect of the dry product layer during the MTM procedure ⇒ requires more investigation.
- Note: 2nd step: "optimization process" failed, but "product quality" OK.

![Graph 2](image)
Case Study V: "Critical Temperature" Setting

- What is the impact of the "critical temperature" setting on cycle design? Judge by SMART data (temperature, resistance) and visual appearance (shrinkage):

  - 2.5% sucrose, 112 20cc vials, 3 ml fill: setting (1) $T_c$: -36°C, (2) $T_c$: -28°C

  - **Case 1** - SMART $T_{\text{target}}$: -39°C, good agreement between MTM and avg. thermocouple data, $T_{\text{max}}$ (MTM): -37°C ⇒ reduction of shelf temperature setting after ~ 10h.
    ⇒ Good cake, resistance according to model behavior (type 1)

  - **Case 2** - SMART $T_{\text{target}}$: -31°C, good agreement between MTM and avg. thermocouple data, $T_{\text{max}}$ (MTM): -33°C.
    ⇒ about 1°C above $T_c$, decrease of resistance data, clear shrinkage

Case Study V: "Critical Temperature" Setting

- What is the impact of the "critical temperature" setting on cycle design when using different concentrated solutions? Judge by SMART data (temperature and resistance) and visual appearance (e.g. shrinkage).

  - 2.5%, 5% and 10% sucrose: 112 vials, 20cc, 3 ml fill, change in collapse temperature setting: higher total solid content may tolerate higher temperature?
Conclusions

✓ SMART freeze dryer technology showed its potential during this preliminary testing phase to become a valuable PAT tool in the future...

...for a better understanding of the freeze drying process.
...to systematically study impact of formulation design or process parameters on product resistance, sublimation rate, etc.

✓ Accuracy of "required input parameters" (e.g. knowledge of $T_c$ or $T_g'$) critical for "successful run".

✓ SMART testing conducted with "simple systems" ⇒ need to gain more experience with complex formulations.

✓ Other available "options" in SMART software need to be tested in the future (e.g. secondary drying option).

✓ Atypical "effects" arising from high solid content or results from PVP need to be studied in more detail (ongoing work).

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References


