MULTISTAGE HEAT PUMP DRYING OF BIO-PROTEIN PARTICLES

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The path in developing a medical product from concept to manufacturing includes parallel execution of 4 main tasks:

- critical path
- safety
- medical utility
- industrialization.
THE CRITICAL PATH IS:

- basic research
- prototype design
- preclinical and clinical trials
- FDA/EU filling and approval
- launch.
THE SAFETY PROCEDURE IS:

- material selection
- in vitro tests
- human-animal tests
- safety check.
THE MEDICAL UTILITY IS:

- *in vitro & PC model evaluation*
- *in vitro animal models*
- *human efficacy evaluation.*
• physical design
• small scale production
• scale-up
• refinement
• mass production.
PHASES OF THE R&D PROCESS FOR A SINGLE MEDICAL PRODUCT

- Patent application
- Acute toxicity
- Pharmacology
- Chronic toxicity
- Phase I clinical trials
- Phase II
- Phase III
- Registration & transparency
- Price
- Reimbursement
- Pharmacovigilance

A medical product

0 yrs 5 yrs 10 yrs 15 yrs 20 yrs

10 years of research 2-3 years of administrative procedures Patent expiry
Innovative and enhanced pharmaceutical powders can be produced using new multistage fluidized bed drying techniques. The dryer operates at temperatures below and above the material freezing point. It combines advantages of sublimation and evaporation and it is a potential alternative for production of heat sensitive powders.
The powders can be produced with enhanced and pre-specified properties. Modeling single and multistage fluidized bed requires changing conditions as much as possible. That can be done and accurately controlled in conditioned cabinets.
THE MAIN OBJECTIVES ARE TO:

• perform multistage drying trials with the spherical proteic particles,

• describe the associated processes,

• control the conditions,

• identify factors effecting moisture content, drying rates and water activity.
Frozen state

Atmospheric freeze drying: sublimation of ice to vapor

Atmospheric medium temperature drying: liquid flow by compression and shrinkage

Evaporation of liquid to vapor

Proteic product matrix and different phases of water during freezing and freeze drying processes

Mechanisms of moisture removal in medium temperature drying of proteic product matrix
1. Compressor
2. Condenser
3. Receiver tank
4. Internal heat-exchanger
5. Expansion valve
6. Evaporator
FREEZE DRYING AIR & REFRIGERATION
FLUID STATE POINTS IN THE P-H CHART

A Saturated vapor
B Slightly superheated gas
C Superheated gas
D Saturated vapor
E Saturated liquid
F Subcooled liquid
G Liquid-vapor mixture
ATMOSPHERIC FREEZE & MEDIUM TEMPERATURE FLUIDIZED BED DRYER

Grosvenor’s chart with the heating and cooling steps to reach the inlet conditions for all runs.
## EXPERIMENTAL CONDITIONS FOR DRYING RUNS

<table>
<thead>
<tr>
<th>Run</th>
<th>$T$, °C</th>
<th>$d_p$, mm</th>
<th>$X_0$, %</th>
<th>$X_f$, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-10/20</td>
<td>2</td>
<td>73.17</td>
<td>5.87</td>
</tr>
<tr>
<td>2</td>
<td>-5/20</td>
<td>2</td>
<td>71.91</td>
<td>5.60</td>
</tr>
<tr>
<td>3</td>
<td>0/20</td>
<td>2</td>
<td>71.77</td>
<td>5.39</td>
</tr>
<tr>
<td>4</td>
<td>-5/20</td>
<td>4</td>
<td>71.38</td>
<td>5.28</td>
</tr>
</tbody>
</table>

Olsztyn, 12 April 2012
BET equation describes the equilibrium moisture content as function of water activity for all runs:

\[ X_e = \frac{X_m \cdot C_m \cdot a_w}{(1 - a_w) \cdot (1 + (C_m - 1) \cdot a_w)} \]
# Water Activity and BET Equation

## Parameters for the Drying Runs

<table>
<thead>
<tr>
<th>Run</th>
<th>$a_{wo}$</th>
<th>$a_{wf}$</th>
<th>$C_m$</th>
<th>$X_m$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>96.7</td>
<td>3.23</td>
<td>2.981</td>
<td>0.027</td>
</tr>
<tr>
<td>2</td>
<td>96.6</td>
<td>3.34</td>
<td>2.590</td>
<td>0.120</td>
</tr>
<tr>
<td>3</td>
<td>96.2</td>
<td>3.03</td>
<td>0.850</td>
<td>0.030</td>
</tr>
<tr>
<td>4</td>
<td>96.8</td>
<td>2.84</td>
<td>2.692</td>
<td>0.035</td>
</tr>
</tbody>
</table>
TYPICAL DESORPTION ISOTHERM FOR
RUN 1 & EXPERIMENTAL DATA POINTS

Graph showing desorption isotherm with data points and a curve.
Fick’s 2\textsuperscript{nd} law for moisture diffusion in batch drying:

\[ r^2 \cdot O_d \cdot \left( \frac{\partial^2 X}{\partial x^2} + \frac{\partial^2 X}{\partial y^2} + \frac{\partial^2 X}{\partial z^2} \right) = \frac{\partial X}{\partial t} \]

Moisture content equation:

\[ X = \frac{6 \cdot [(X_0 - k) - X_e]}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp(-n^2 \cdot O_d \cdot t) + X_e \]

Inverse drying time equation:

\[ O_d = \frac{4 \cdot D_e}{d_p^2} \]

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The measured moisture content and drying time were used to determine the constants for moisture content equation and inverse drying time equation. Nine terms were used for the series since this provided a difference less than $2\times10^{-6}$ from the next term.
KINETICS PARAMETERS FOR THE DRYING RUNS

<table>
<thead>
<tr>
<th>Run</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>T, °C</td>
<td>-10/20</td>
<td>-5/20</td>
<td>0/20</td>
<td>-5/20</td>
</tr>
<tr>
<td>$O_{d1}$</td>
<td>0.573</td>
<td>0.627</td>
<td>1.250</td>
<td>0.779</td>
</tr>
<tr>
<td>$O_{d2}$</td>
<td>0.840</td>
<td>1.340</td>
<td>1.430</td>
<td>1.440</td>
</tr>
<tr>
<td>$D_{e1} \times 10^{-10}$, m$^2$/hr</td>
<td>1.591</td>
<td>1.741</td>
<td>2.505</td>
<td>8.651</td>
</tr>
<tr>
<td>$D_{e2} \times 10^{-10}$, m$^2$/hr</td>
<td>2.333</td>
<td>3.722</td>
<td>3.972</td>
<td>16.00</td>
</tr>
<tr>
<td>$X_{e1}$, %wb</td>
<td>52.29</td>
<td>64.68</td>
<td>8.82</td>
<td>17.09</td>
</tr>
<tr>
<td>$X_{e2}$, %wb</td>
<td>0.50</td>
<td>1.50</td>
<td>1.50</td>
<td>1.50</td>
</tr>
<tr>
<td>$X_c$, %wb</td>
<td>57.29</td>
<td>61.01</td>
<td>19.23</td>
<td>22.09</td>
</tr>
<tr>
<td>$t_c$, hr</td>
<td>1.00</td>
<td>1.50</td>
<td>1.50</td>
<td>2.00</td>
</tr>
</tbody>
</table>

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PREDICTED AND EXPERIMENTAL MOISTURE CONTENT VERSUS TIME FOR MULTI-STAGE DRYING
The drying rates were determined using the previous equations for moisture content and inverse drying time and equation for cumulative water removal:

\[
N(0 \leq t \leq t_f) = \int_0^{t_f} \left[ \frac{6[(X_0 + k) - X_e]}{\pi^2} \right] \times \\
\times \sum_{i=1}^{\infty} -O_d \cdot \exp(-n^2O_d t) \right] dt
\]
TWO STAGE DRYING RATES

for run 1

for run 2

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TWO STAGE DRYING RATES

for run 3

for run 4

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PREDICTED AND EXPERIMENTAL MOISTURE CONTENT VERSUS TIME FOR MULTI-STAGE DRYING
CONCLUSIONS

- Multistage drying trials were done to study effect of conditions on drying rates and dryer capacity.

- The BET equation describes well the protein sorption isotherms and Fick’s second law holds satisfactorily for sublimation and evaporation drying.

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CONCLUSIONS

- Multistage drying produces protein powders with enhanced quality by sublimation and improves dryer capacity by changing to evaporation stage to increase the mass diffusivity or drying rate.

- The highest COPs occur for minimum difference between condensing and evaporating temperature.
Thank you for your attention!