



LyoFlux[®] - TDLAS Water Vapor Mass Flow Monitor

Turnable Diode Laser Absorption Spectroscopy Sensor Control Unit



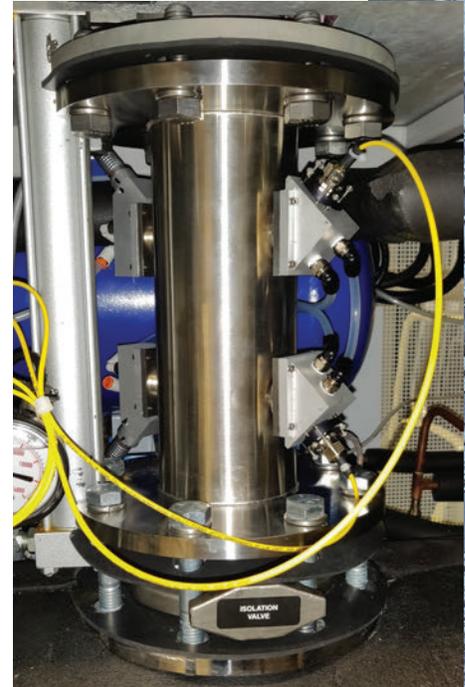
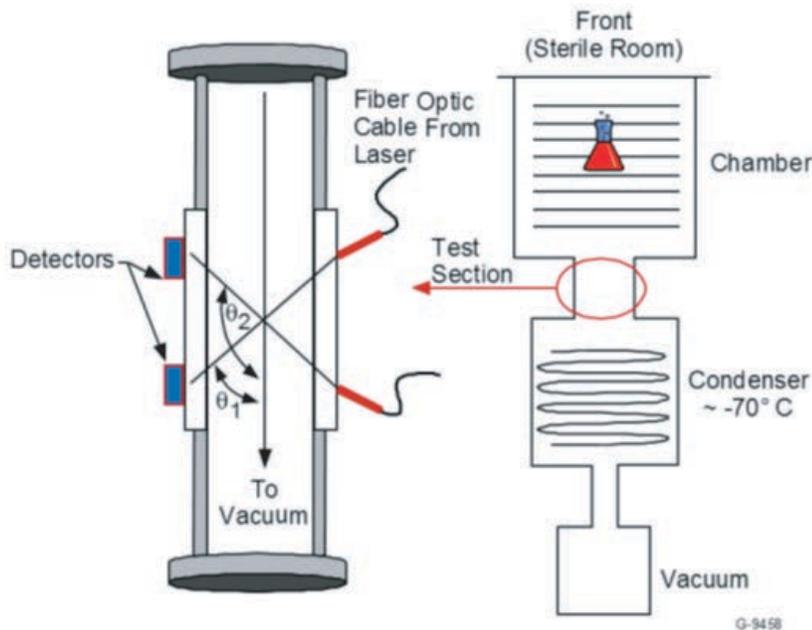
- Process Analytical Technology (PAT) instrument for monitoring pharmaceutical freeze-drying water vapor mass flow (dm/dt)
- Applicable to lab, pilot and production scale lyophilizers
- Measures water vapor temperature (T_{gas}), number density [H_2O] and flow velocity (v); calculates and reports batch average dm/dt
- Non-intrusive, continuous mass balance determination
- Applications:
 - Primary & secondary drying endpoints
 - Batch average K_v , R_p , T_b , T_o , P_{ice} , L_{ice} determinations
 - Lyophilizer equipment capability limit determination
 - Development of process Quality by Design (QbD) operating space
 - Provides data needed to investigate process deviations
- QbD modeling included with instrument software; enables rapid cycle development
- Applications supported by peer-reviewed technical publications
- Low maintenance, permanent calibration, 24/7/365 operation
- Direct communication with and control by SP lyophilizers, data and alarm integrated with LyoS 2.0
- Used by both expert and novice lyophilization process developers

Points of Contact:

Bill Kessler, kessler@psicorp.com, t: 978-738-8253 | Emily Gong, egong@psicorp.com, t: 978-738-8289

20 New England Business Center | Andover, MA 01810-1077 | t: 978-689-0003 | f:978-689-3232 | www.psicorp.com

LyoFlux[®] - Specifications



Freeze Dryer Measurement Interface

Parameter	Specification
Measurement range	
H ₂ O density	10 ¹⁴ to 1.75x10 ¹⁶ cm ⁻³ (equals 3 mTorr to 500 mTorr at 273K)
H ₂ O velocity	0 to Mach 0.9
H ₂ O Mass Flow Rate	~1E-3 – 2.5 grams/second
Response time	60 seconds
Accuracy	
Relative error H ₂ O Mass Flow Rate	≤7.0%
Relative error Total H ₂ O Removed	≤7.0%
(Average, 3-shelf sublimation test: shelf temp -10, -5, 0°C, pressure: 65, 100, 200 mTorr)	
Measurement	
Principle	TDLAS (Tunable Diode Laser Absorption Spectroscopy)
Sample Gas	Nitrogen (N ₂) and Water Vapor (H ₂ O)
Measurement Gas	Water Vapor (H ₂ O)
Measurement angles	45° & 135°
Measurement location	In spool between chamber and condenser, upstream of isolation valve
Minimal spool length	FD dependent
Calibration verification using ice slab tests	6-months
Sensor Operation	
Zero velocity offset determination	Automatic or manual start
Integration of "Total H ₂ O Removed"	Automatic or manual start
Chamber pressure input	Automatic input
Start data logging	Automatic or manual start (data stored to comma separated variable (CSV) data file)
Alarming	Displayed on sensor GUI and freeze dryer GUI
Alarm logging	Yes, in freeze dryer alarms log
Trending	Real-time display on sensor GUI and freeze dryer GUI
End point detection of primary drying	Per user interpretation of [H ₂ O]
End point detection of secondary drying	Per user interpretation of [H ₂ O]
Pharmaceutical Compliance	
21CFR Part 11 compliant	No
CIP/SIP compliant	Yes

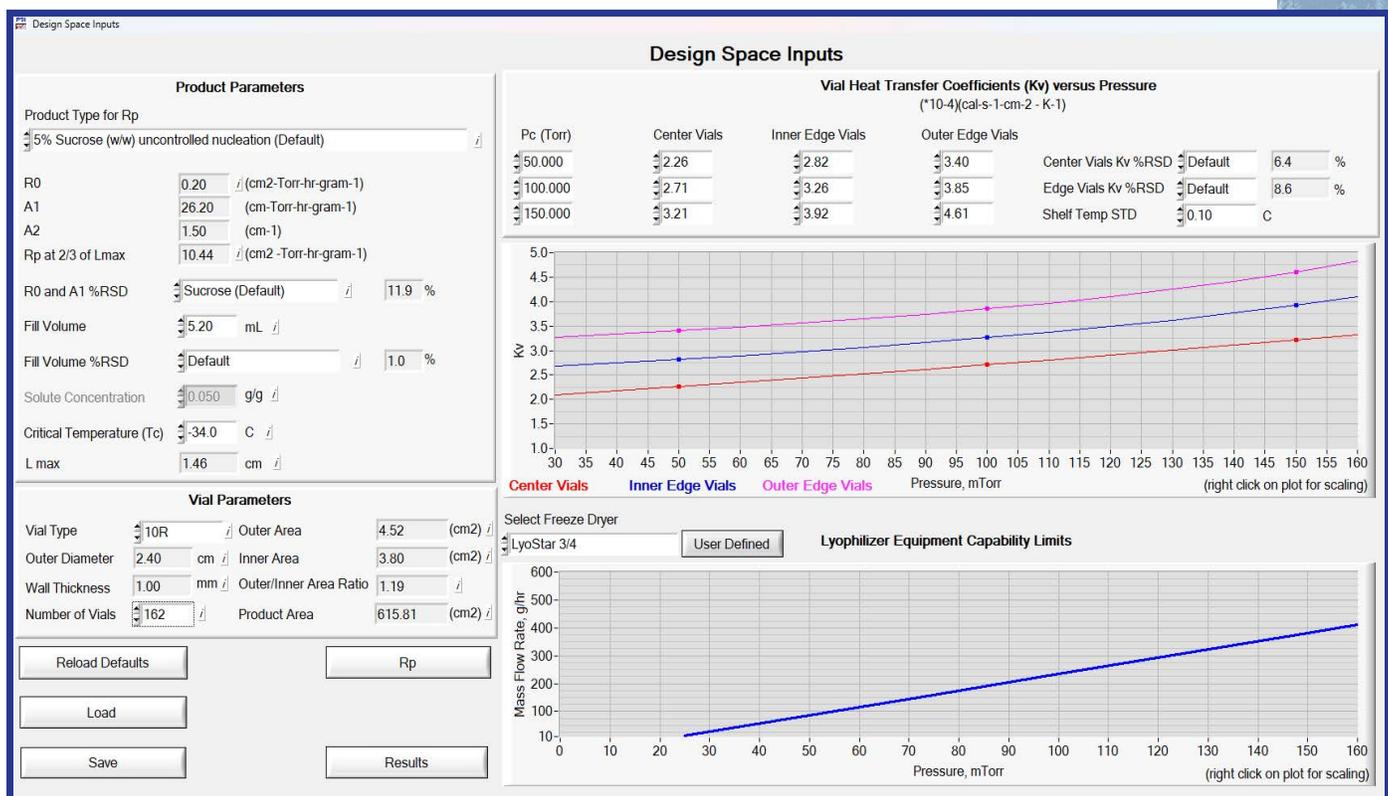
LyoFlux® - Primary Drying Process Model of Heterogeneous Drying



NOW PART OF THE LYOFUX 200 MASS FLOW RATE MONITOR INSTRUMENT CONTROL SOFTWARE

Features:

- Intuitive Graphical User Interfaces (GUI) enabling computational-based process development
- Enables thought experimentation: *e.g. What happens to the product temperature and drying time if I change the shelf temperature or chamber pressure?*
- Separates vials into three classes to predict drying rates and product temperatures (center, inner edge and outer edge) using differentiated and statistical variations in model inputs
- Predicts product temperature as a function of vial class and drying time
- Predicts % of vials exceeding the user defined critical temperature
- Predicts the % of vials not completing primary drying
- Creates QbD knowledge space plot for each calculated “drying experiment”
- Pull-down menus for “typical” product and process parameters or user-defined inputs
- Allows fitting of Rp vs dry layer thickness experimental data to enable product temperature and drying rates predictions as a function of process time
- Ability to store inputs and model results to document process development calculations
- Includes capability limits for Lyostar 3/4 and LyoConstellation S10 & S20 lyophilizers



Process development model Input GUI, accounting for process heterogeneity by vial class (center, inner edge and outer edge vials)

LyoFlux® - Primary Drying Process Model of Heterogeneous Drying (cont.)

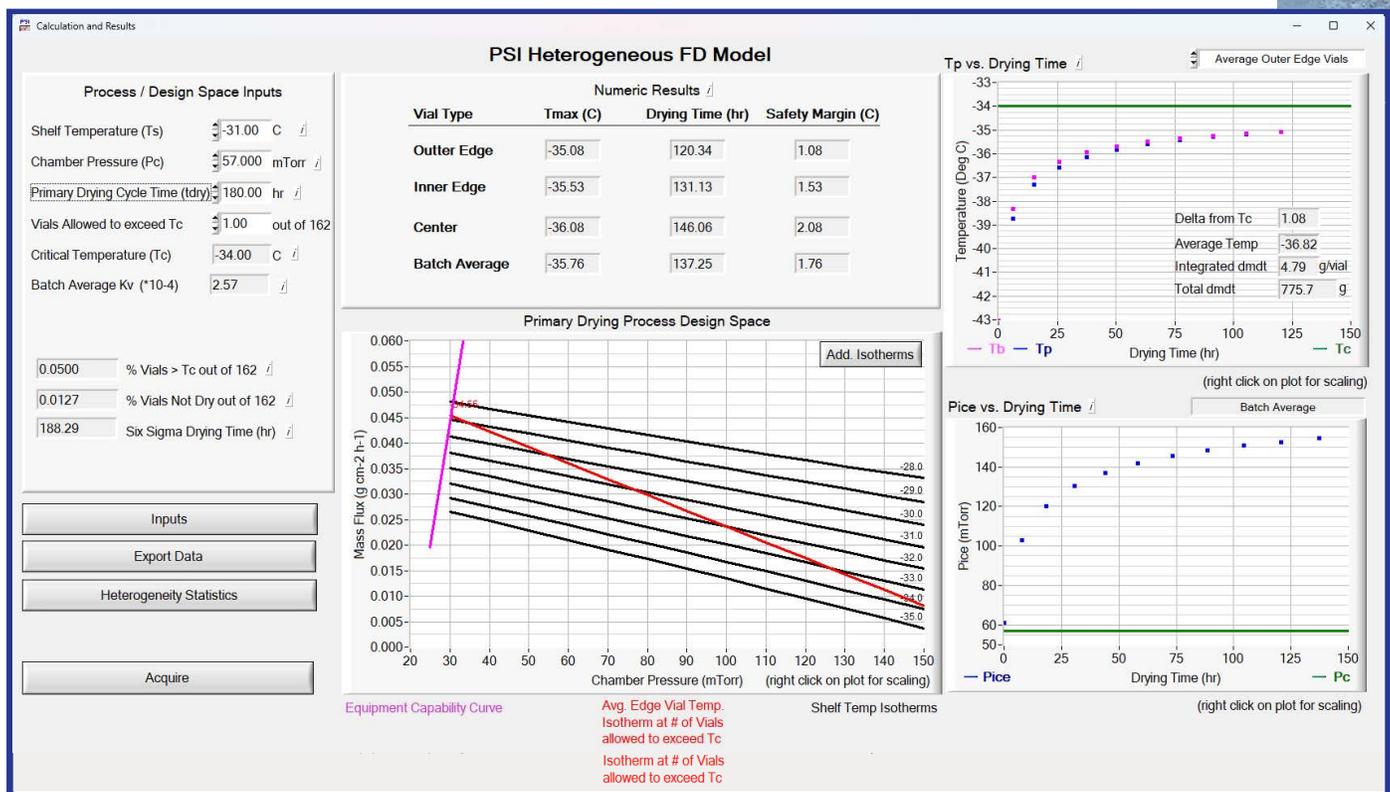


Value Proposition:

- Process modelling tool is now part of the standard LyoFlux 200 software package
- Supports process development by both lyophilization experts and non-experts
- Model performance verified by comparison to experimental results drying excipient and industry representative formulations - peer reviewed publication:
 - Bogner, R., Gong, E., Kessler, W., et al. "A Software Tool for Lyophilization Primary Drying Process Development and Scale-up including Process heterogeneity, I: Laboratory-Scale Model Testing", AAPS PharmSciTech (2021) 22:274.
- Facilitates both laboratory process development and process scale-up when used in combination with the LyoFlux TDLAS-based water vapor mass flow rate monitor
- Accurate product temperature predictions ($\pm 1^\circ\text{C}$)
- Accurate product drying time predictions ($\pm 10\%$) for primary drying
- Modelling procedure and QbD design space consistent with FDA expectations

Core Applications:

- Laboratory scale process development and process scale-up
- Process anomaly investigations



Process development model Results GUI, accounting for process heterogeneity by vial class (center, inner edge and outer edge vials)



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