Freeze Drying Heat and Mass Transfer: Factors in Dry Cake Resistance by Manometric Temperature Measurement

Xiaolin (Charlie) Tang[1,3], Steven L. Nail[2,4], and Michael J. Pikal[1]

[1]School of Pharmacy, University of Connecticut; [2] Department of Industrial and Physical Pharmacy, Purdue University

[3]Present: Formulation Development, Centocor, Inc. [4]Lilly Research Laboratories, Eli Lilly & Co

Purpose: To evaluate the factors that impact dryer cake resistance in primary drying using Manometric Temperature Measurement (MTM) technique.

Methods: Freeze drying of different materials at different concentrations and freeze drying conditions were performed using a FTS Dura-Stop/Dura-Top freeze dryer (FTS) with MTM software installed. The MTM equations were fitted to MTM data to obtain dry layer resistance (R_p) and product temperature (T_p). The freeze drying processes were designed to ensure acceptable cake appearance for all the products.

Manometric Temperature Measurement

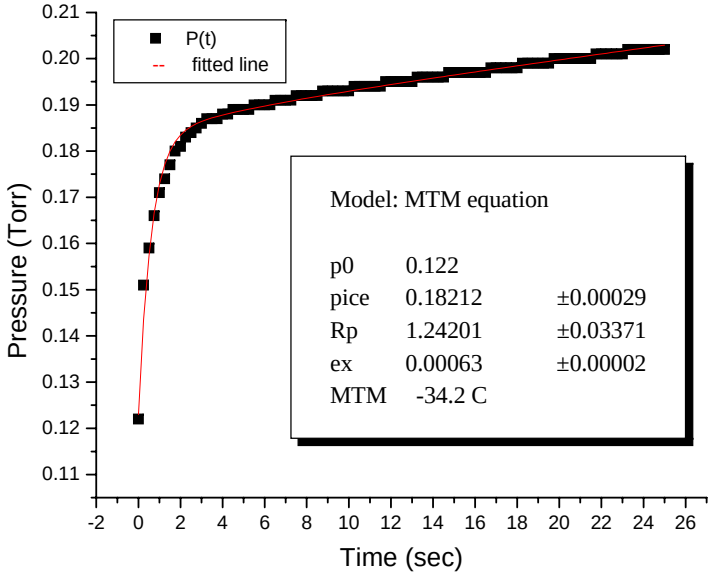
MTM equations:

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

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

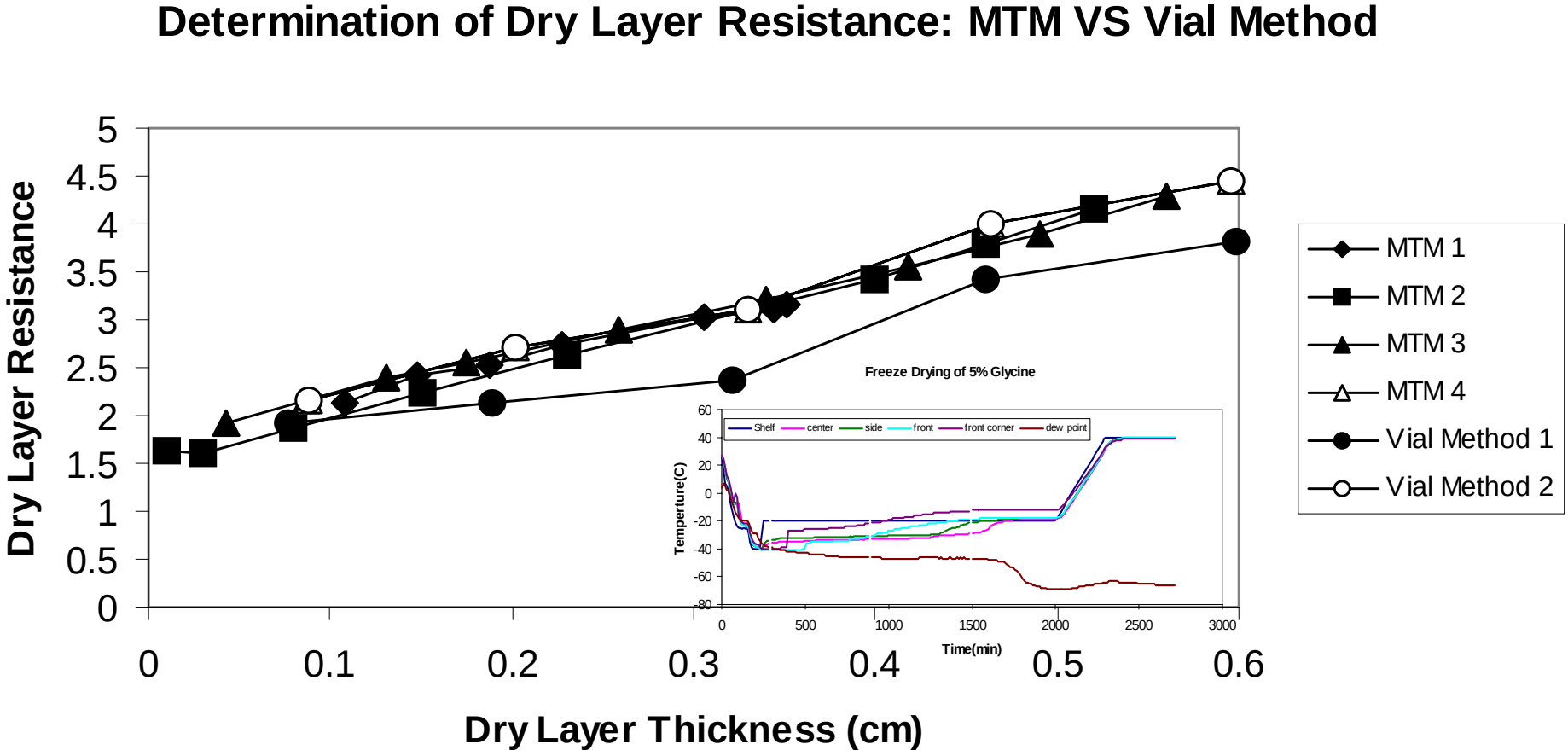
P_{ice}=pressure of ice (fit),
MTM=ice temperature calc from P_{ice}
P_0=chamber pressure (set)
N=# of vials (known),
A=inner area of vials (known)
T_s=shelf temperature (set)
V=chamber volume (known)
R_p=product resistance (fit)
L'=ice thickness (calculated)
X=a constant (fit)
ΔT=temperature difference between sublimation surface and bottom (by fit)

The Vapor Pressure Data and Fitted Curve

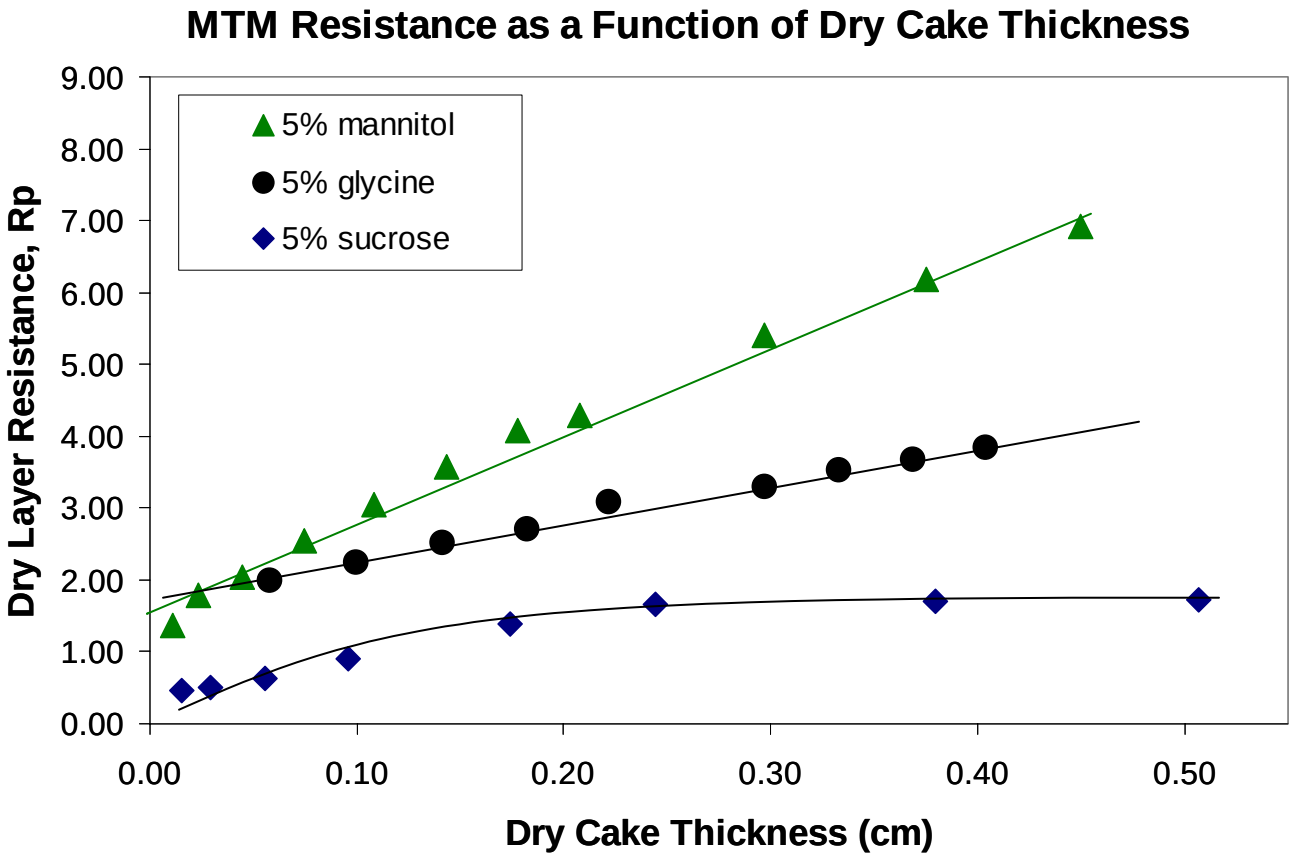


[1]: Nathaniel Milton, Michael J. Pikal, Michael L. Roy and Steven L. Nail. "Evaluation of Manometric temperature measurement as a method of monitoring product temperature during lyophilization", *PDA Journal of Pharmaceutical Science & Technology*, **5** (1)**,** 7-16 (1997)

Use Manometric Temperature Measurement (MTM) to Determine Dry Cake Resistance



Dry Cake Resistance for Different Materials



High dry cake resistance:

- High product temperature
- Slow primary drying

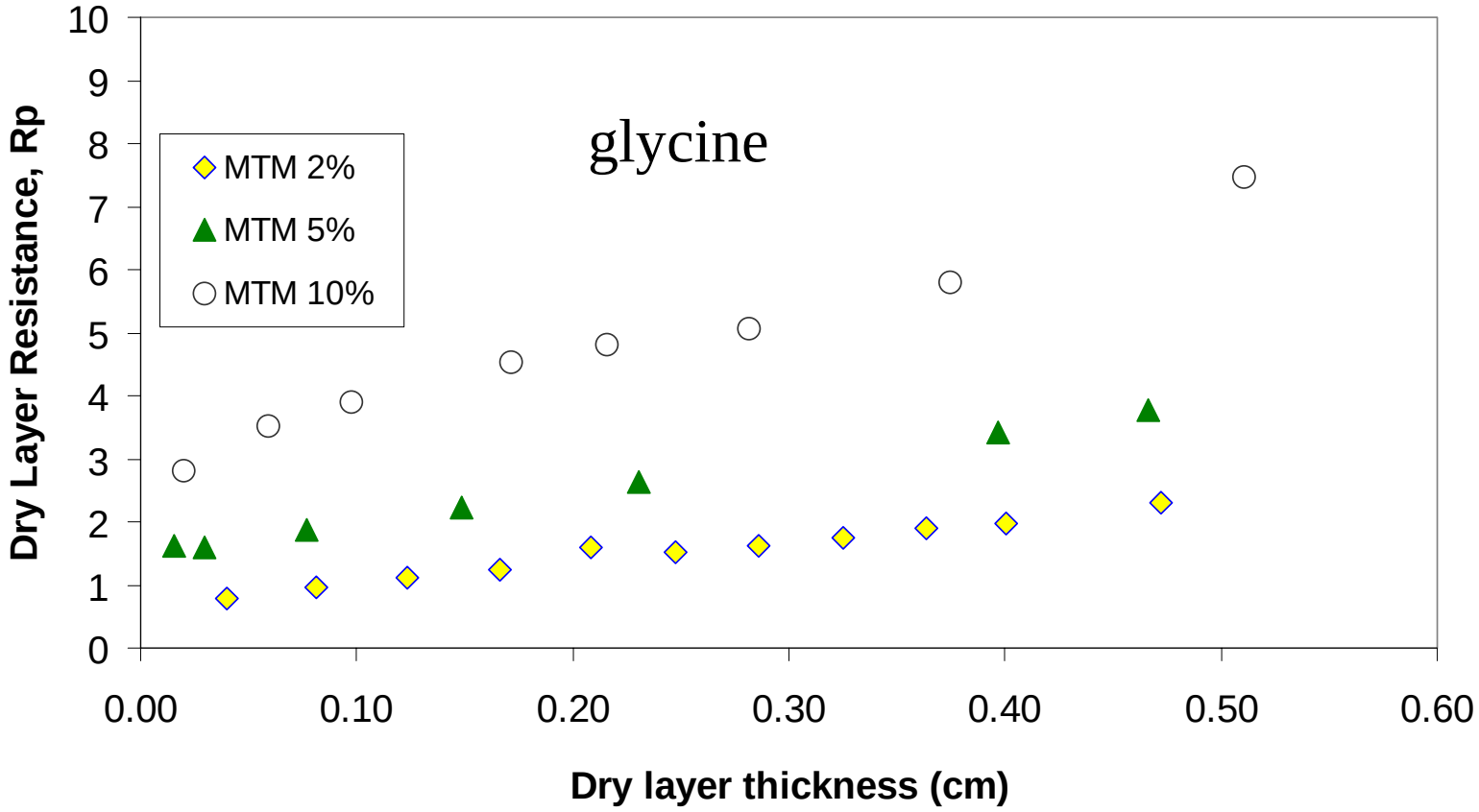
Beneficial to have small dry cake resistance

- Too small dry cake resistance may cause "blow out" in primary drying

Crystalline product has "linear" dry cake resistance behavior while amorphous product usually has "plateaus off" behavior

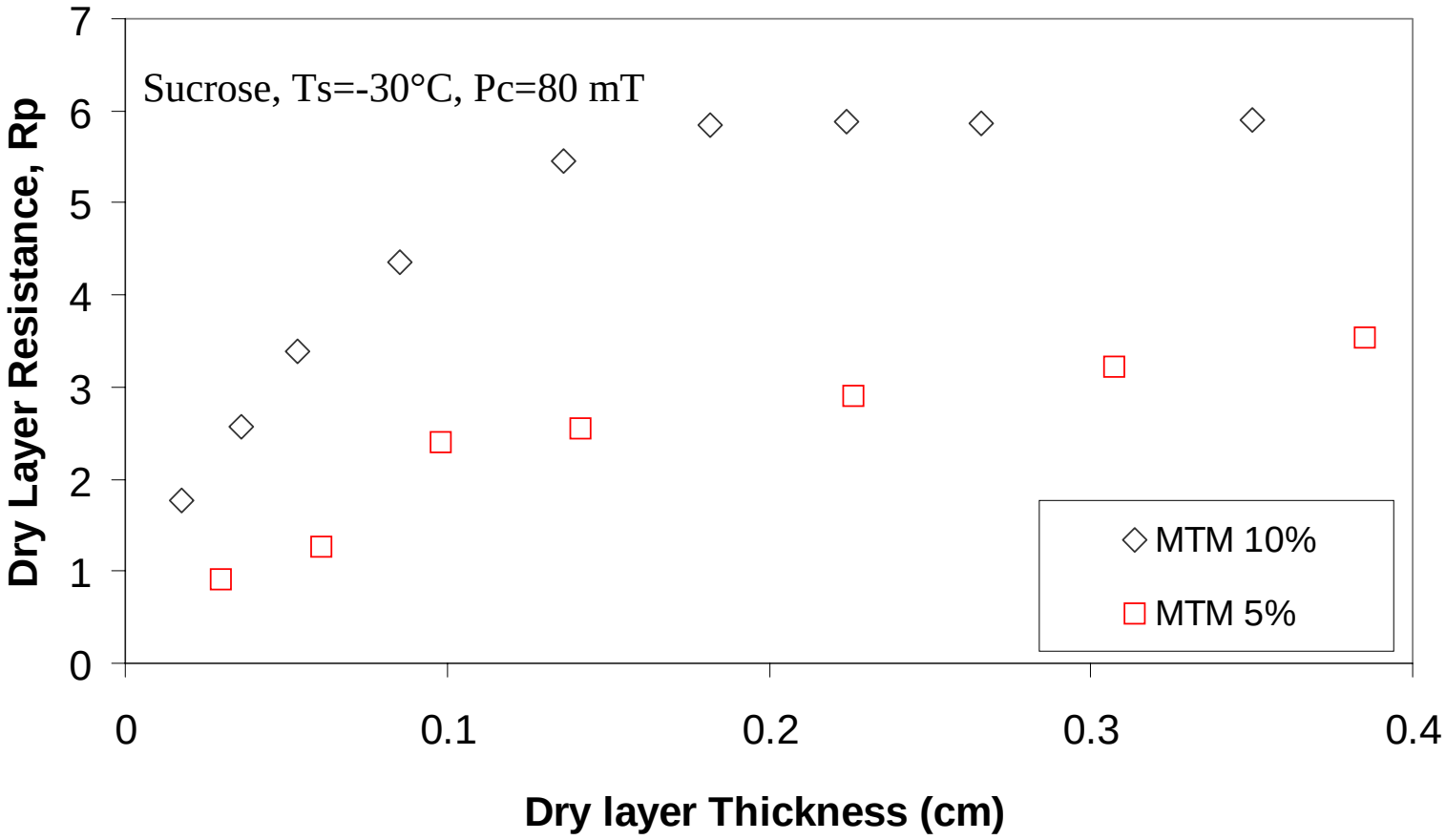
Under the same freeze drying conditions: 5% sucrose has lower product temperature and needs shorter primary drying time than 5% mannitol

Effect of Concentration on Dry Cake Resistance



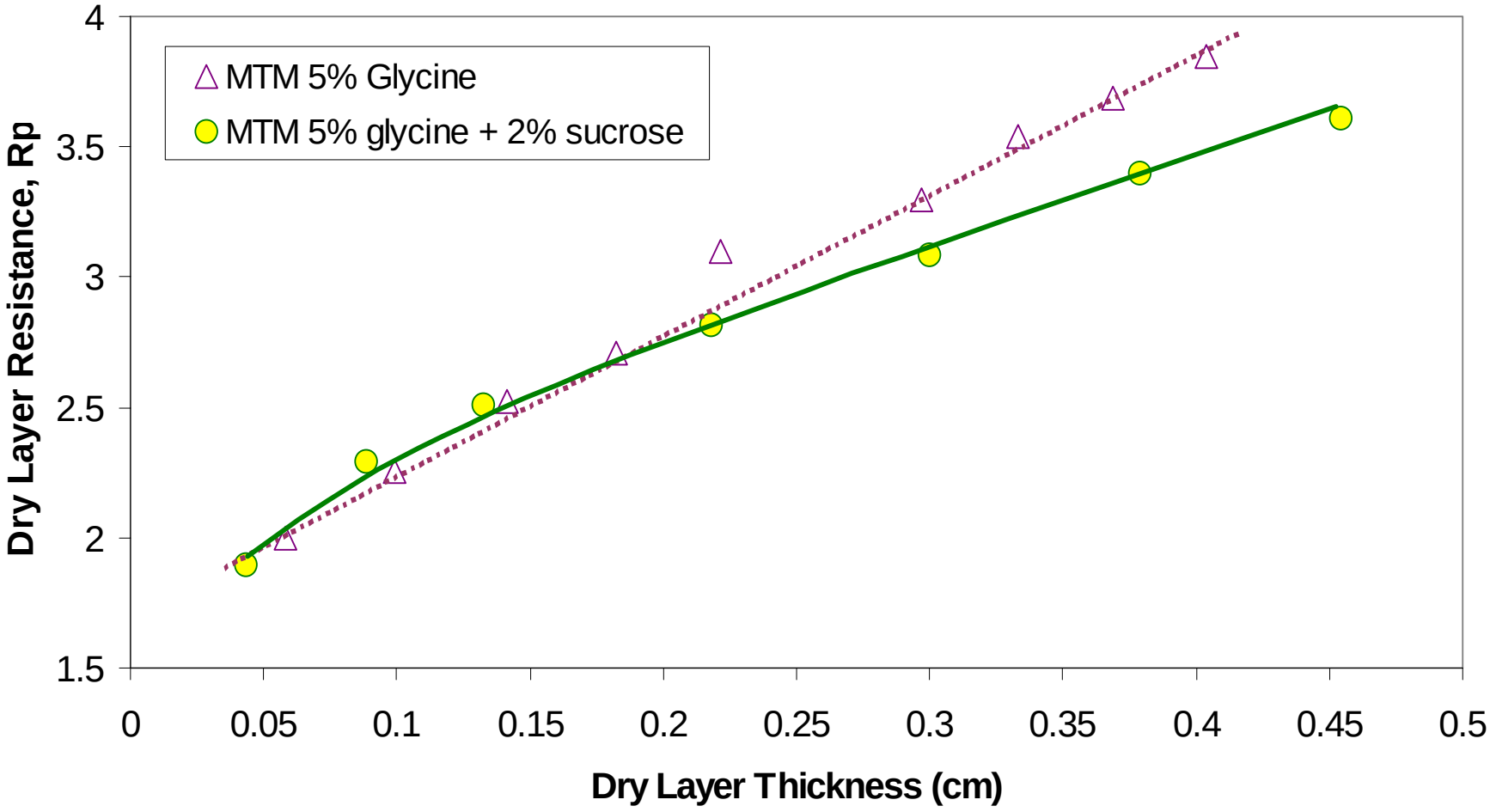
- "Linear" dry cake resistance behavior at all concentrations
  - Product temperature increase with primary drying progressing
- Dry cake resistance increase with concentration
  - More difficult to freeze dry high concentration formulation

Effect of Concentration on Dry Cake Resistance



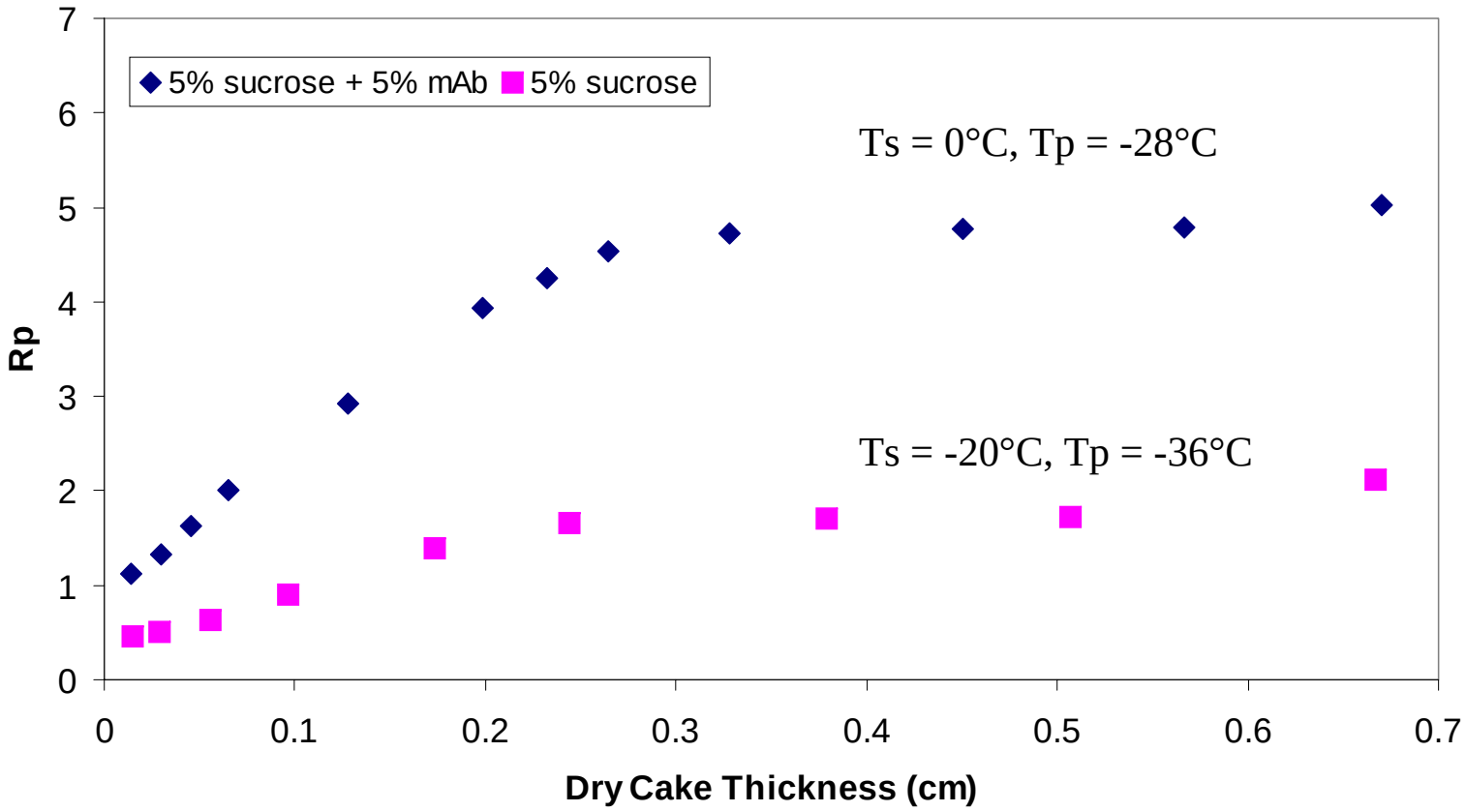
- "Plateau-off" dry cake resistance behavior at all concentrations
  - Product temperature stable in primary drying
- Dry cake resistance increase with concentration
  - Difficult to freeze dry high concentration formulation

Effect of Concentration on Dry Cake Resistance



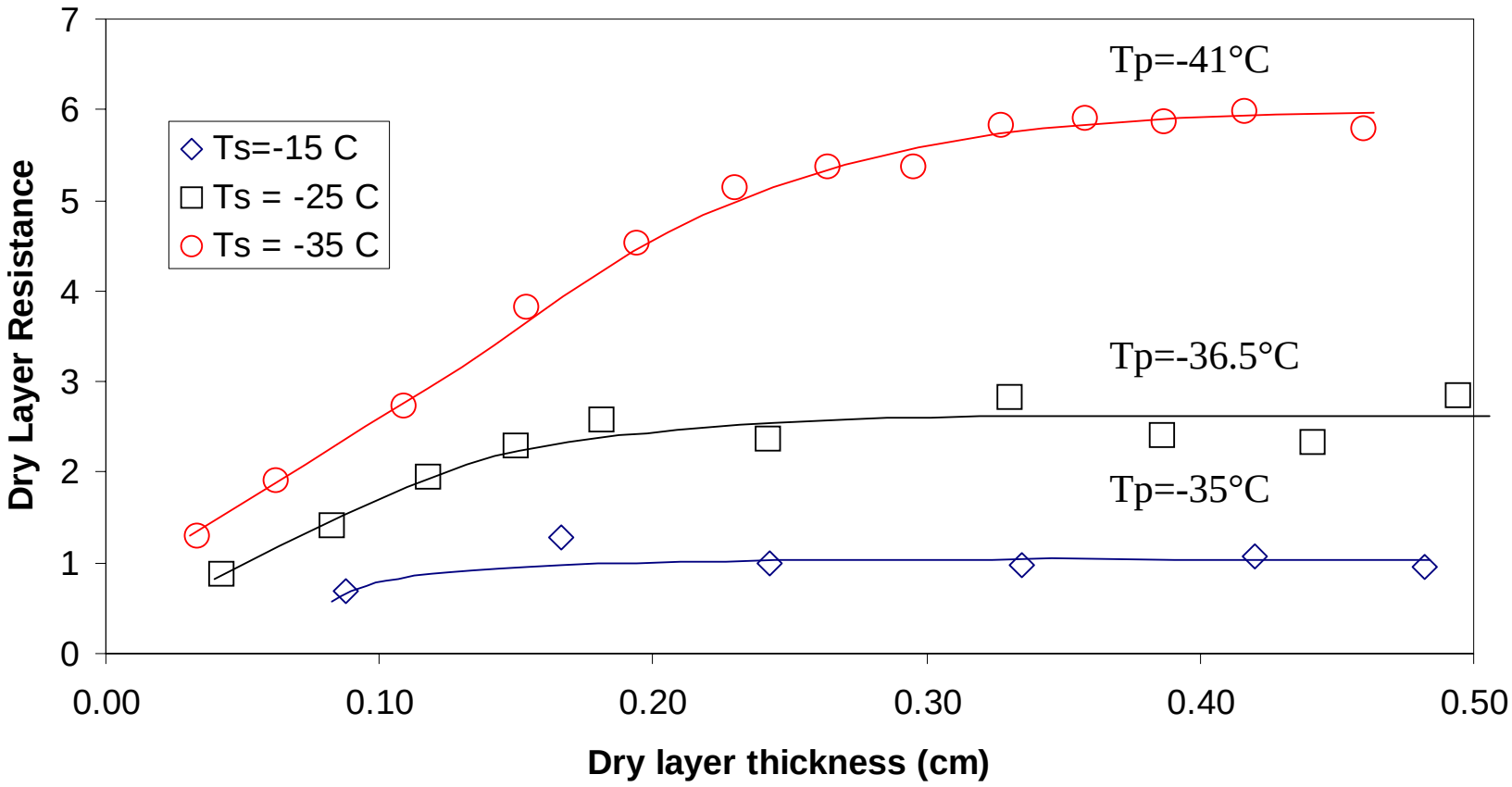
Addition of amorphous material to crystalline product does not increase the dry cake resistance

Effect of Concentration on Dry Cake Resistance



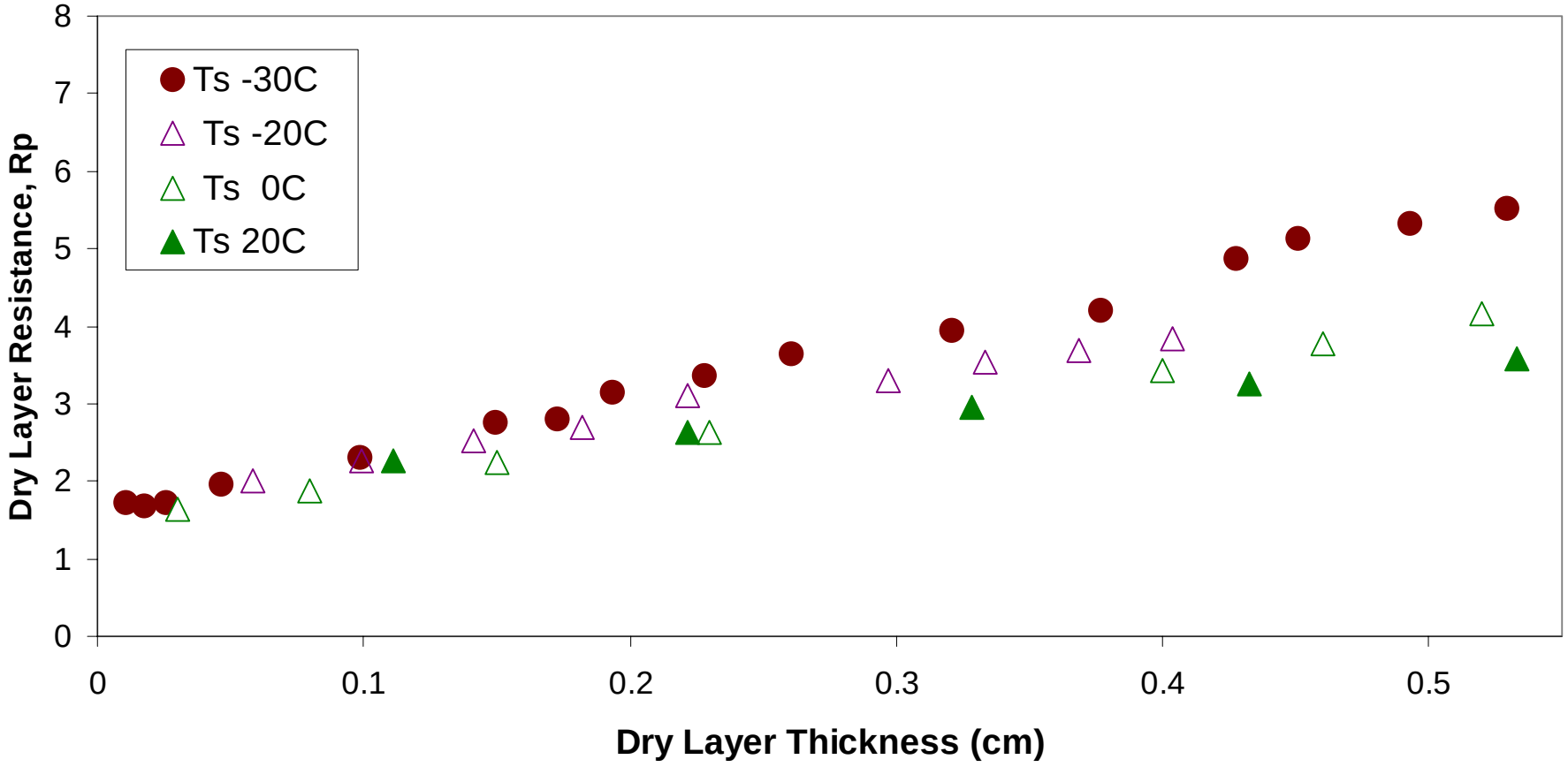
Addition of mAb (amorphous) to sucrose (amorphous) dramatically increases the dry cake resistance

Dry Layer Resistance at Different Shelf Temperature for 5% Sucrose



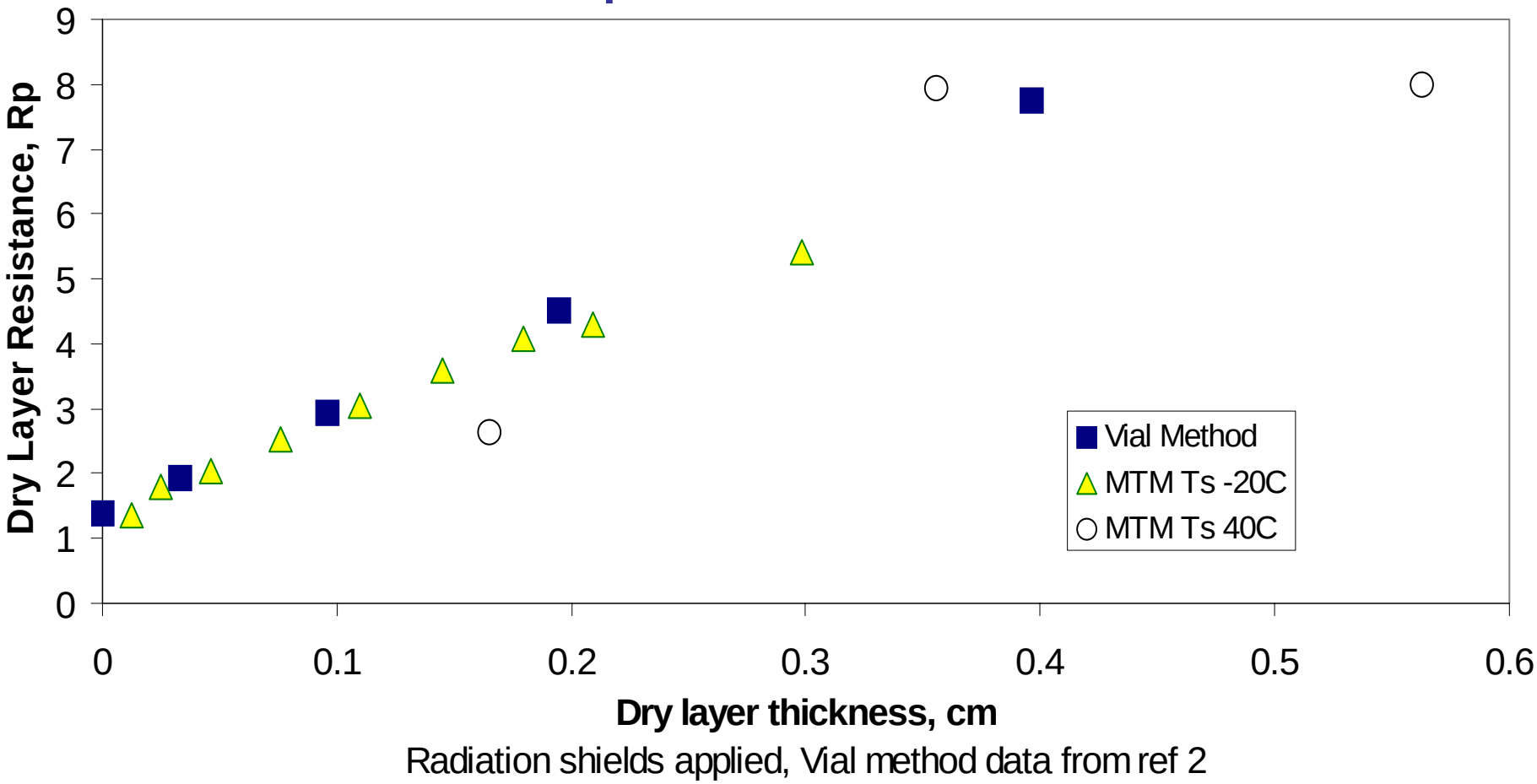
Sucrose dry cake (amorphous product) resistance dramatically decreases with increase of shelf temperature/product temperature

Dry Product Resistance at Different Shelf Temperature for 5% Glycine



Glycine dry cake resistance slightly decreases with increase of shelf temperature/product temperature

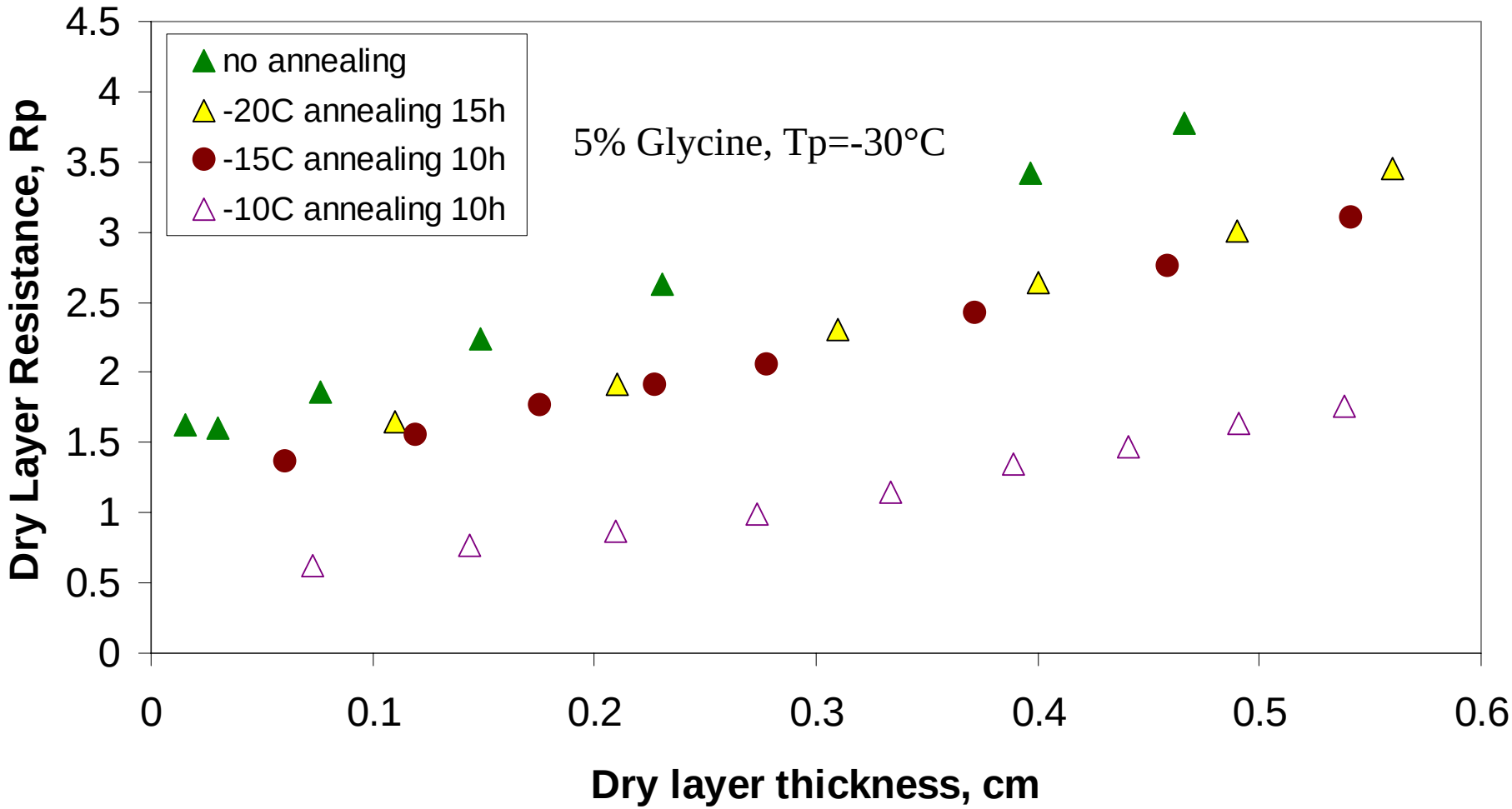
Dry product Resistance for 5% Mannitol Vial Method Compare with MTM Method



Radiation shields applied, Vial method data from ref 2

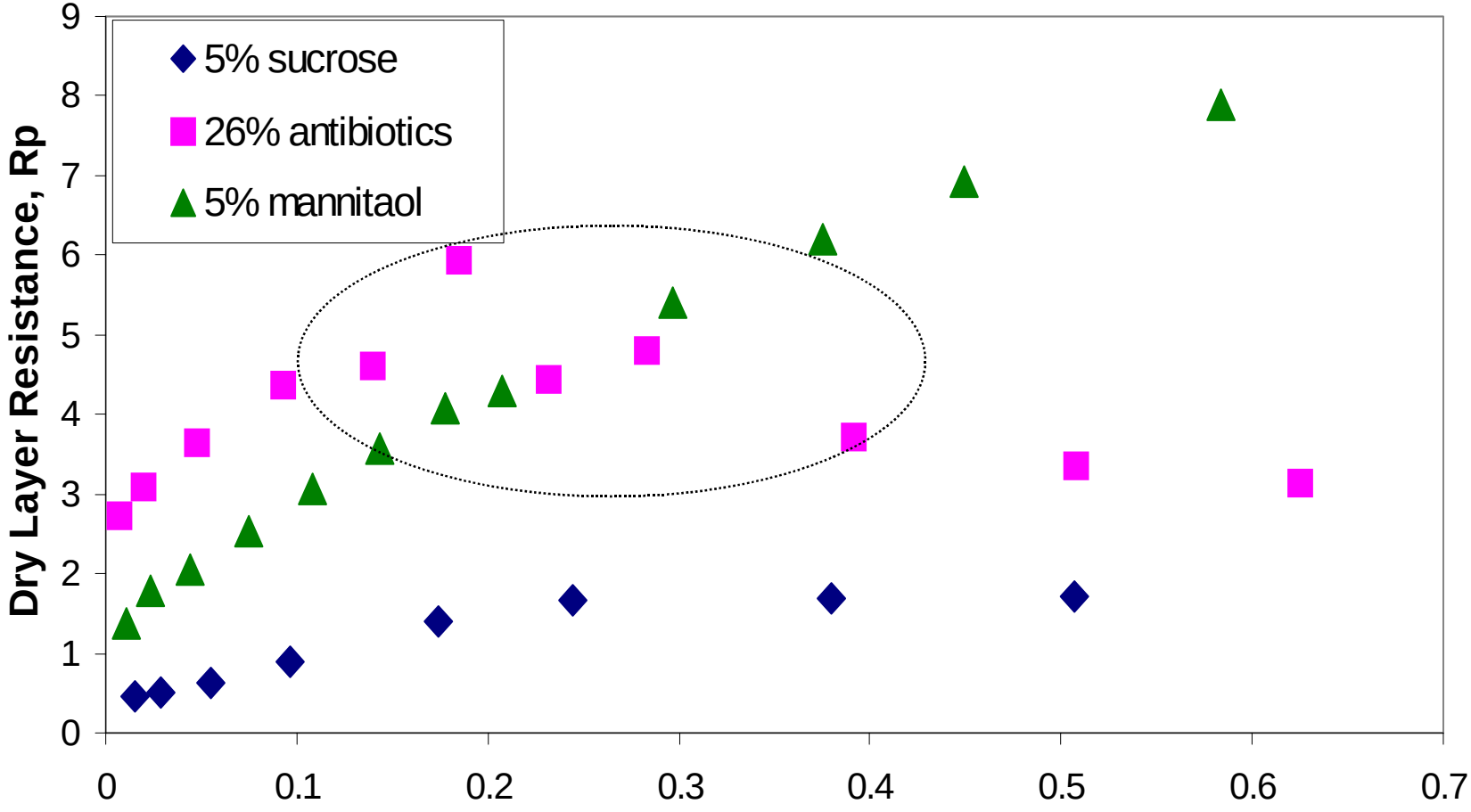
Mannitol dry cake resistance no significant change with increase of shelf temperature/product temperature

Effect of Annealing on Dry product Resistance



Dry cake resistance dependent on annealing conditions (annealing temperature and time)

Micro-collapse by MTM Dry product Resistance



The antibiotics formulation showed micro-collapse

Conclusions

- **The properties of the solutes including the solute concentrations have major impact on the mass transfer during primary drying.**
- **Modification of dry cake resistance by freeze drying process design is case dependent.**
- **The manometric temperature measurement (MTM) technique is very useful tool to study the heat flow and mass transfer during primary drying.**

Acknowledgments

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Centocor, Inc.