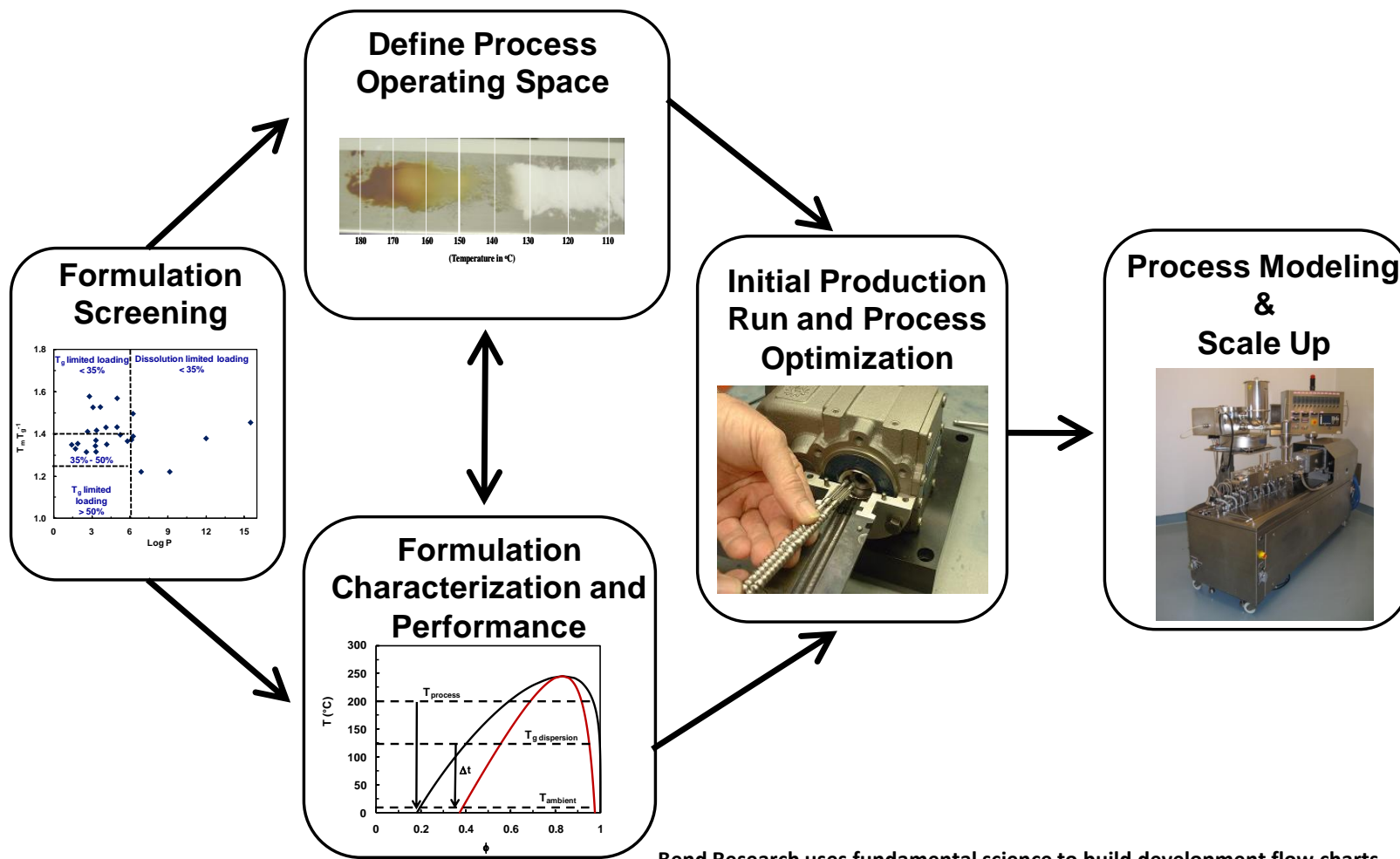


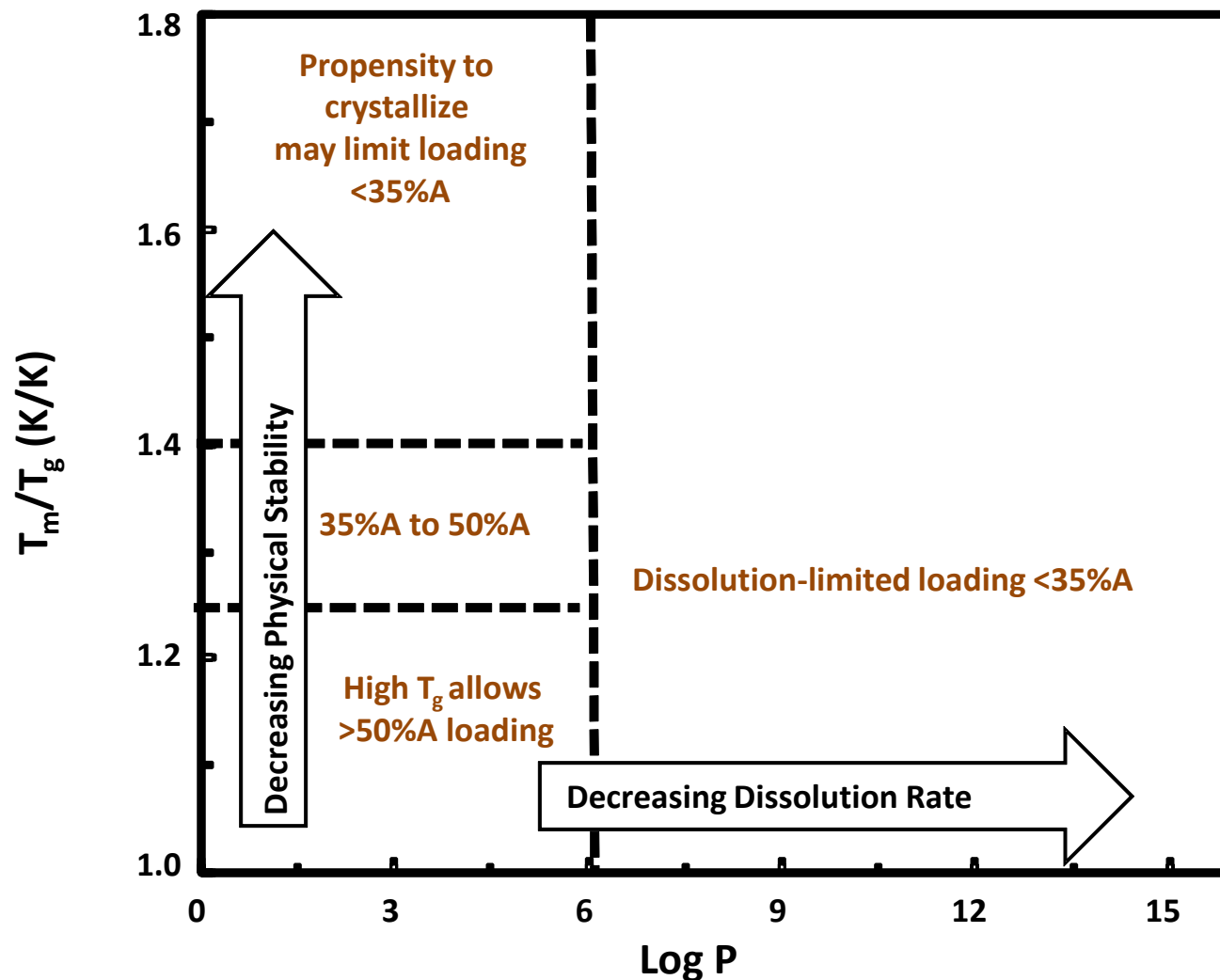
HME Formulation Selection And Process Development

Example Formulation And Process Development Flowchart



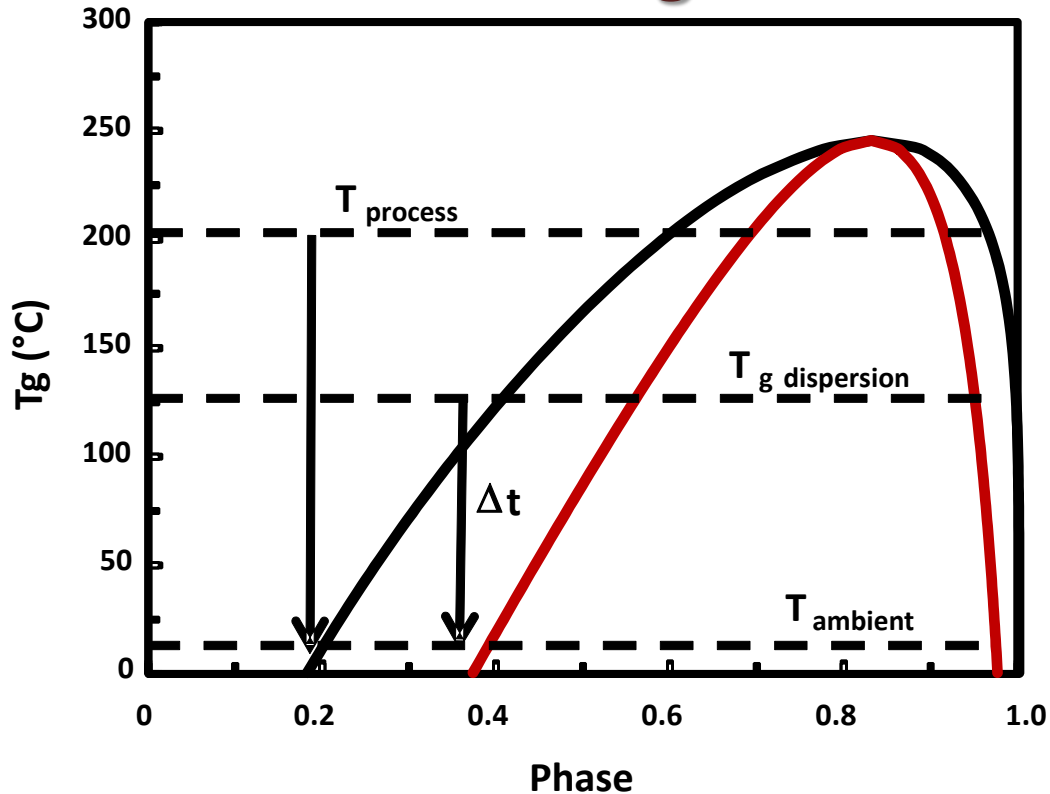
Bend Research uses fundamental science to build development flow charts. These flow charts are continuously improved as Bend Research works on difficult compounds. To learn more, please contact us at info@bendresearch.com or call 800.706.8655. Page 1

Example Compound Property/Formulation Map



Friesen, D.T.; Shanker R.M.; Crew, M.D.; Smithey, D.T.; Curatolo, W.J.; and Nightingale, J.A.S., Hydroxypropyl Methylcellulose Acetate Succinate-Based Spray-Dried Dispersions: An Overview, *Mol. Pharm.*, 5:6(2006)1003-1019.

Example Formulation Characterization: Phase Diagrams

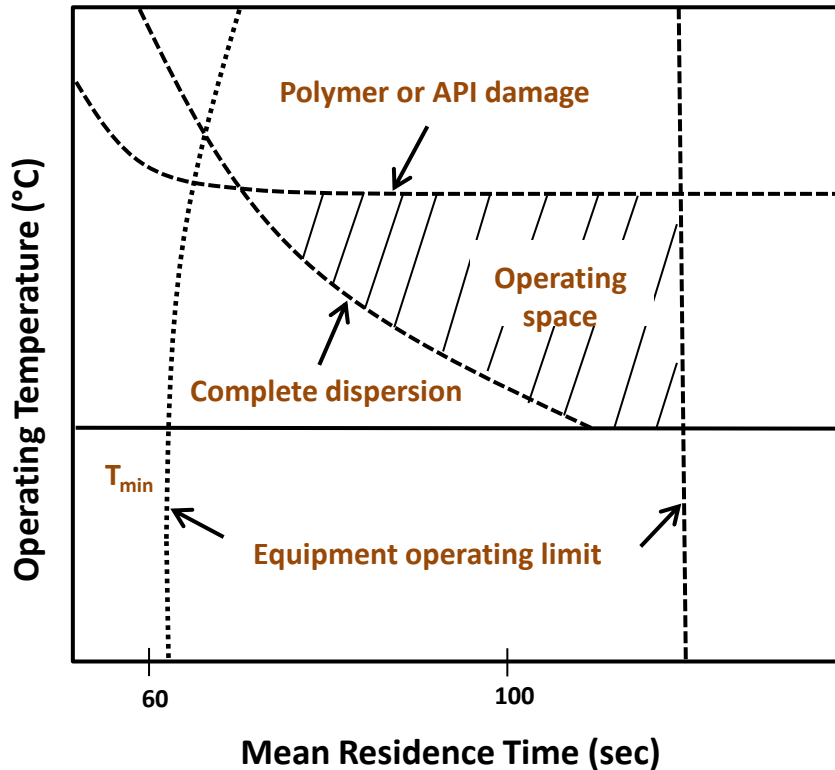


Example conclusion from this analysis: Loading limit for miscible systems

- or -

Identify need to fast quench rate to kinetically trap molecular dispersion for immiscible systems

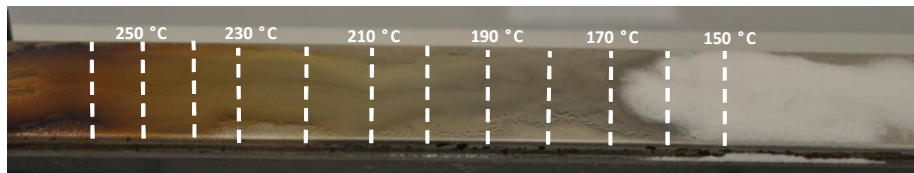
Example Processing Operating Space



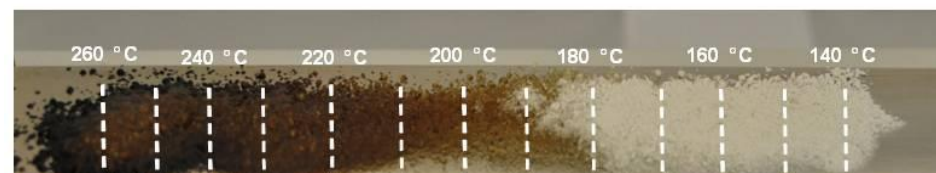
Process Constraints

- Define upper limit for processing temperature
 - API degradation = $f(\text{temperature})$
 - API - polymer temperature-gradient experiment to determine browning point and polymer degradation as a $f(\text{time})$
- Determine residence-time distribution (RTD)
 - $f(\text{feed rate, screw design, screw speed})$
 - Narrow RTD needed for temperature-sensitive API – use 99% residence time?
- Additional tools to identify processing space: differential scanning calorimetry (DSC), polarized light microscopy (PLM), solid-state nuclear magnetic resonance (NMR) spectroscopy

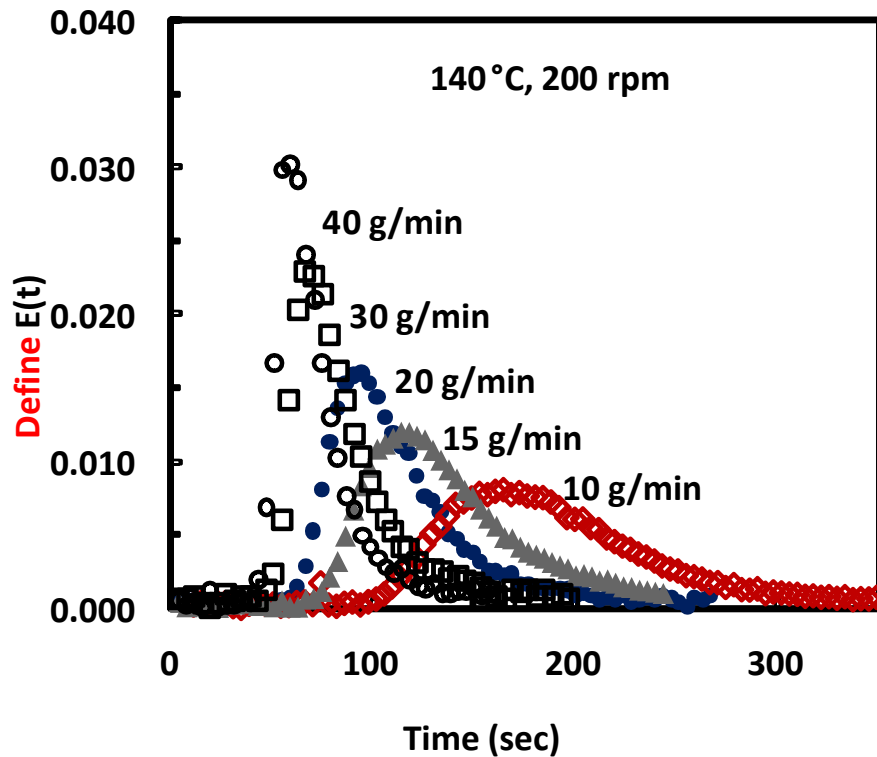
PVP-VA64 Process Temperature 140°C to 200°C



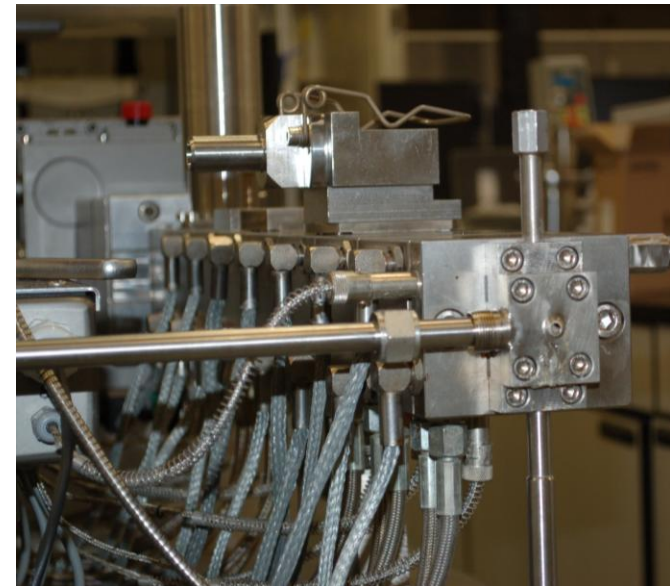
HPMCAS-MG Process Temperature 150°C to 175°C



Example Residence Time Of PVP-VA64 In A 18-mm Twin-Screw Extruder *As a function of feasibility rate*



250-mg pulse of titanium dioxide



18-mm Leistritz Twin-Screw Extruder
With Raman Probe