# A Decade's Experience Delivering Clinical and Commercial Supplies using Fully Continuous Hot Melt Extrusion

Session V: Continuous Processing and Enhanced Process Control: The Realization of QbD

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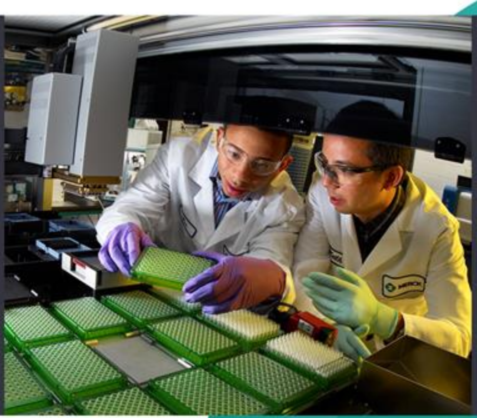

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# Presentation Overview

- Brief introduction to hot melt extrusion (HME)
- Merck's HME history
- HME processing options:  batch vs. continuous
- Compare/contrast to continuous blending/compression
- Use of PAT for HME in development (RTDs) & production (waste gate)
- Process development for HME
  - Use of development data to establish relationship between process parameters & responses
  - Use of modeling to predict process responses
- Control strategy definition for HME
- Batch definition for HME
- Summary & conclusion
- Acknowledgements

# Hot Melt Extrusion (HME) Overview

- Hot melt extrusion applications:
  - Generating amorphous solid dispersions
    - solubility enhancement
    - food effect mitigation
  - Controlled release
  - Taste masking
  - Abuse-deterrence

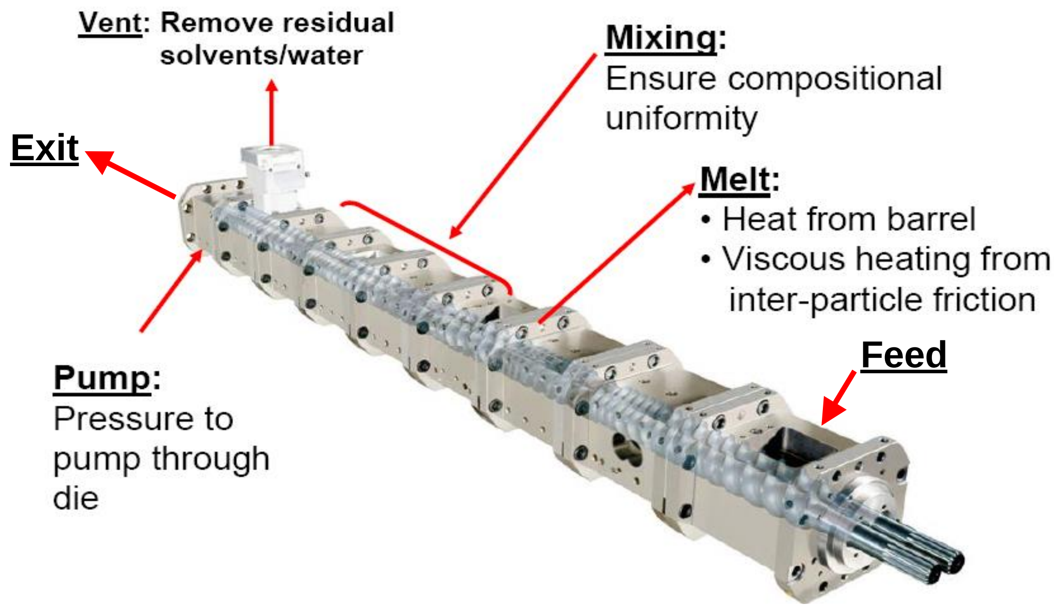
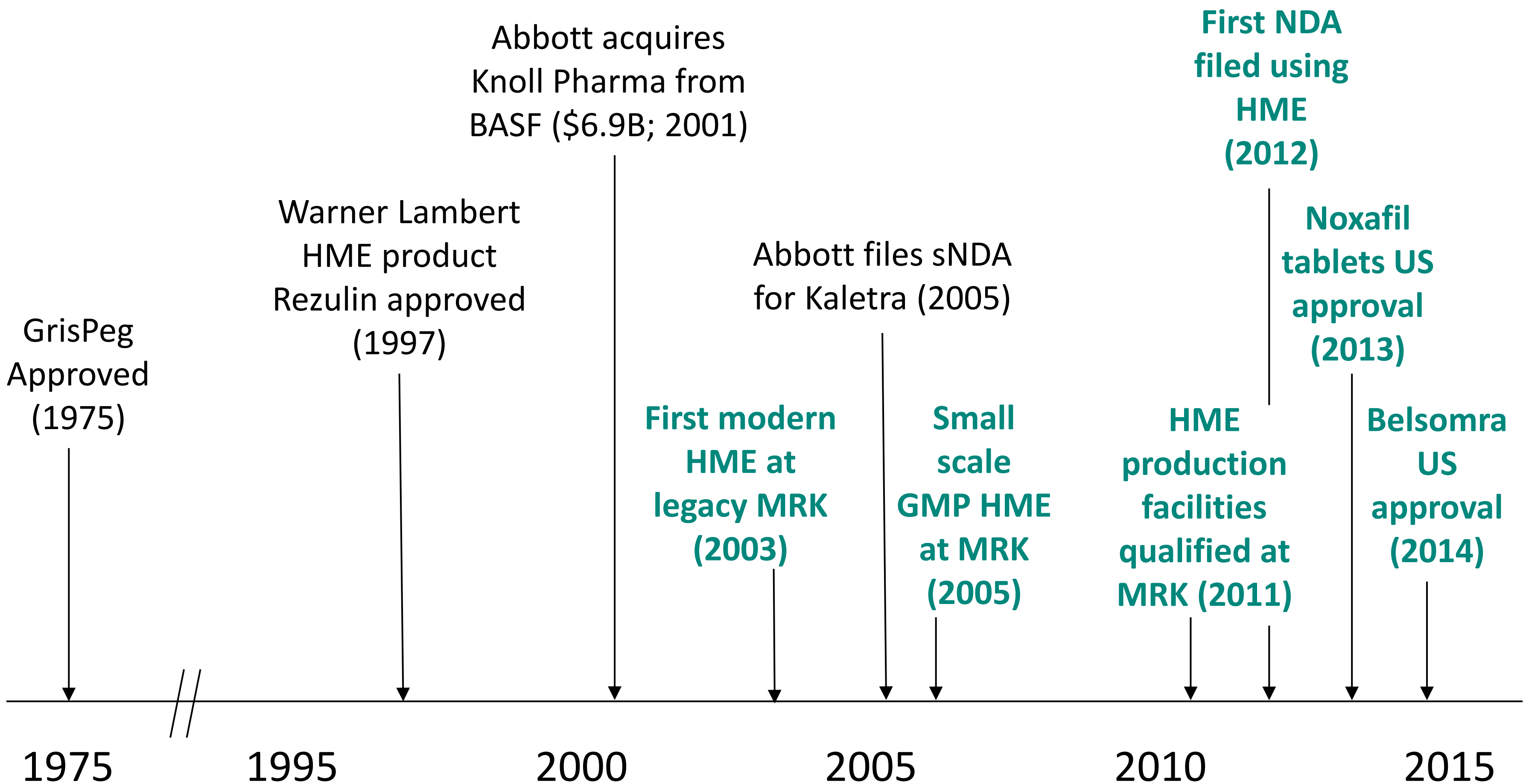



Image courtesy of American Leistritz Extruder Corp

# Timeline of Solid Dispersions and HME in Industry and Merck



# Merck HME Products



*former Merck product


Belsomra®
(suvorexant) CIV
5, 10, 15, 20 mg tablets

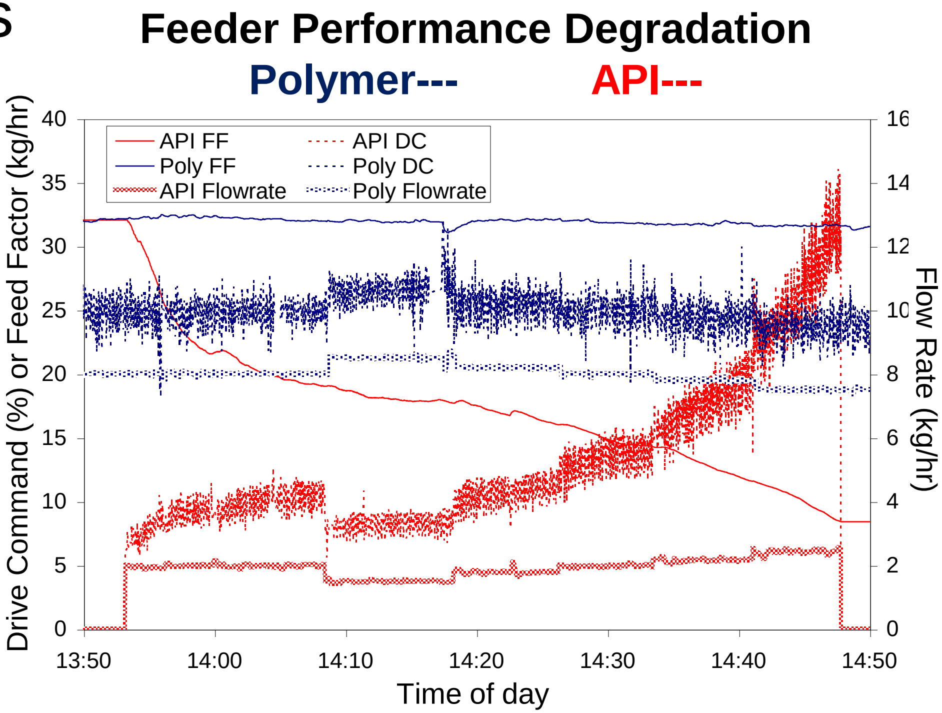
# HME Processing Options

- Upstream Process:
  - Continuous feeding of individual components
  - Pre-blending then feeding
- Downstream Process:
  - Milling, Blending, Direct Compression
  - Encapsulation
  - Injection Molding/Direct Shaping
  - Spheronization
- Wide spectrum of options between fully independent unit operations and fully continuous process

# HME Upstream Processing:
# Batch vs. Continuous & Decision to Preblend

- Technical & cost considerations for choosing the upstream process

– API/polymer feeding trials →
  - Low Tg/highly compressible materials are challenging to feed robustly over long periods of time
  - Preblending = easier feeding




– Cost analysis of pre-blending versus individual feeding
  - Low-medium volume products were typically cost neutral
  - High volume products benefit from individual feeding

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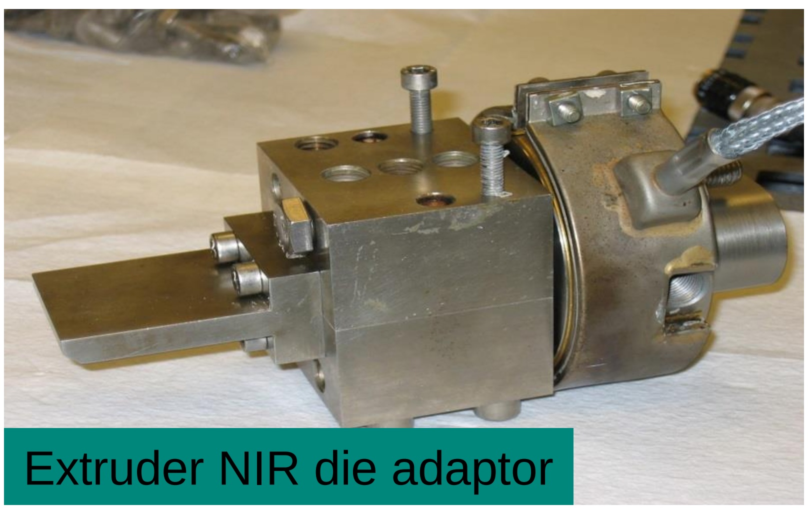
# HME vs. Continuous Blending/Compression

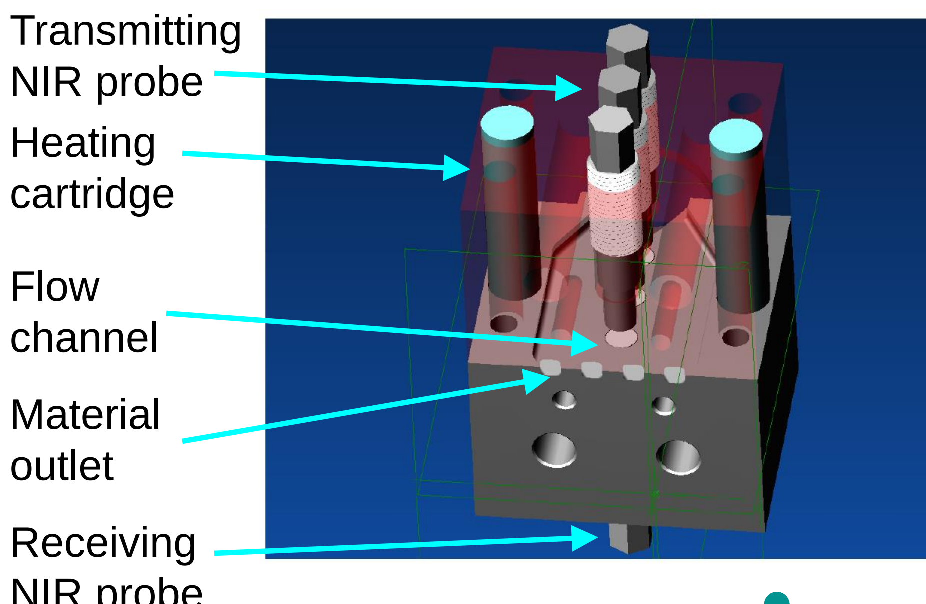
| Similarities to Traditional Continuous Manufacturing | Differences from Traditional Continuous Manufacturing |
|---|---|
| Residence time distributions leveraged for process development | HME has potential failure modes at each end of the residence time distribution range – inadequate mixing & degradation |
| PAT utilized for process monitoring/control | Control strategy definition may be different for HME – process responses such as Tmelt used |
| Batch definition is a key consideration when defining the process | A combination of batch & continuous unit operations may make up the process train |

# PAT Platform for HME – Inline NIR

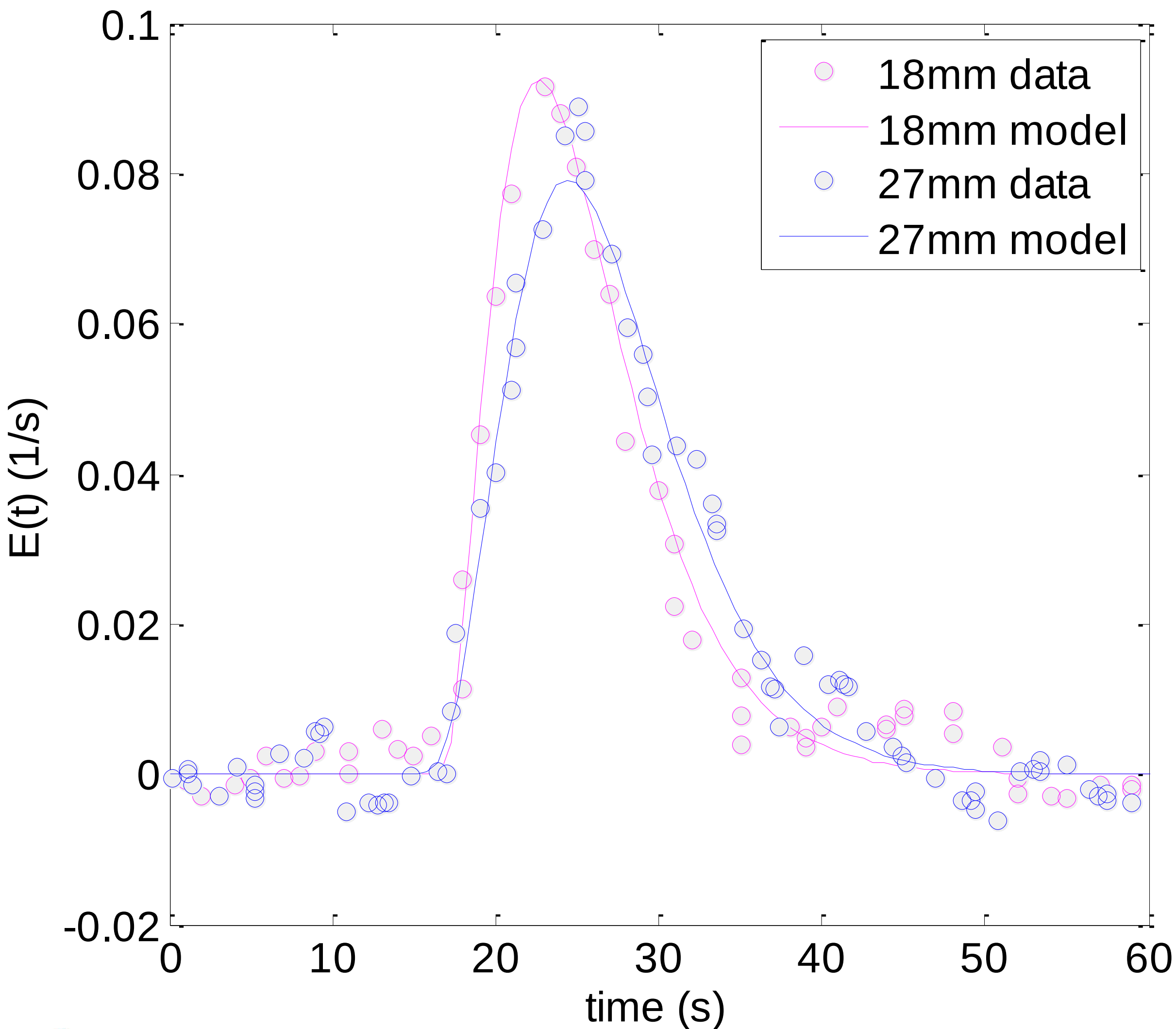
- NIR signal transmitted through extrudate at exit of extruder
- Online readout of formulation composition every ~5 sec
- Used to detect and isolate bad product during routine production
- Used to measure Residence Time Distributions (RTDs) during process development



Extruder NIR die adaptor



# Use of PAT During Development – RTD Measurement




| Scale (mm) | 18 | 27 |
|---|---|---|
| Mass flow rate (kg/hr) | 7.0 | 23.7 |
| Screw speed (rpm) | 380 | 380 |
| Mean residence time (s) | 25.7 | 26.7 |
| StDev residence time (s) | 5.4 | 3.6 |
| Lag time (s) | 16.7 | 15.0 |
| "Mixers in series" | 3.1 | 4.6 |
| Time constant (s) | 8.8 | 12.0 |

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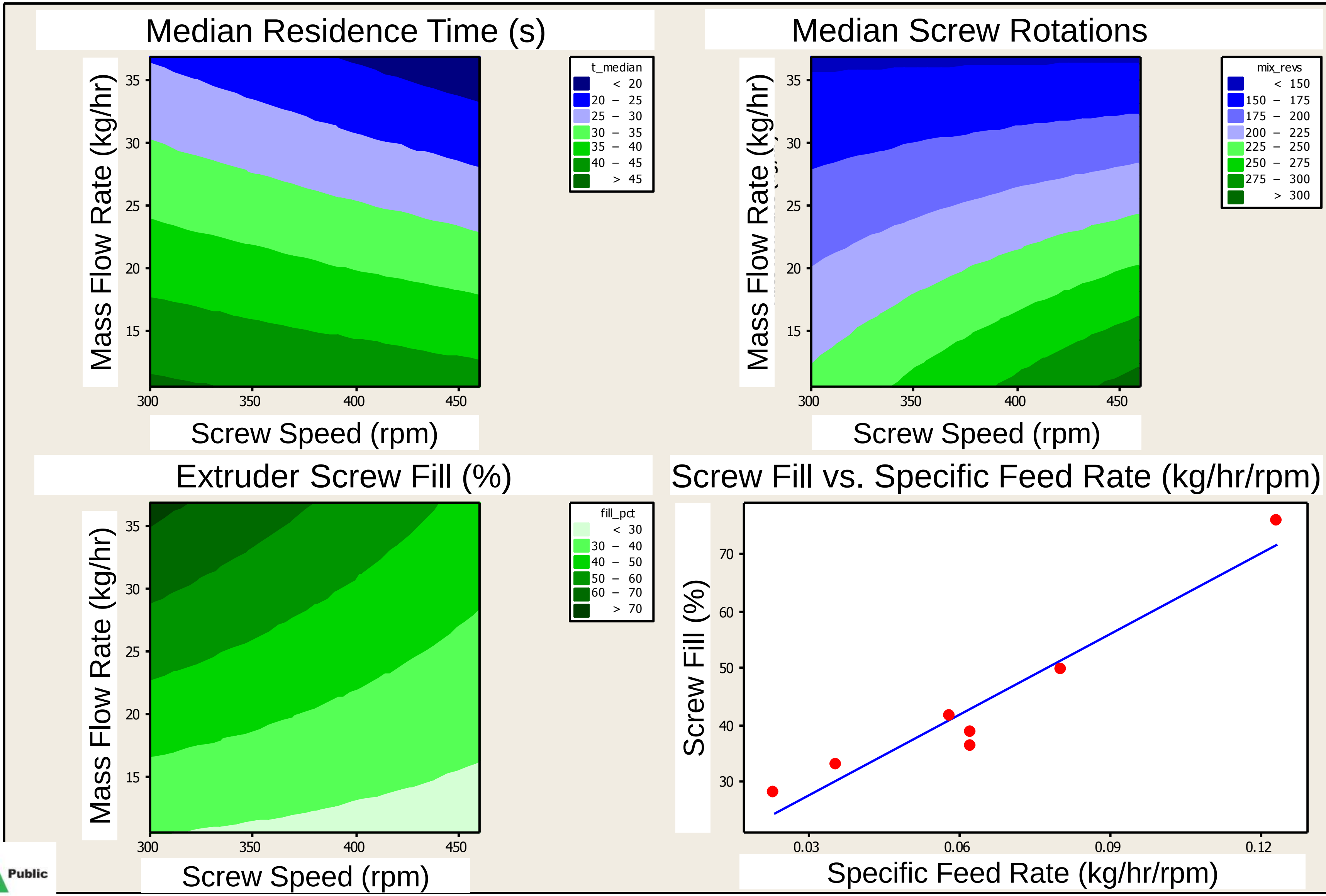
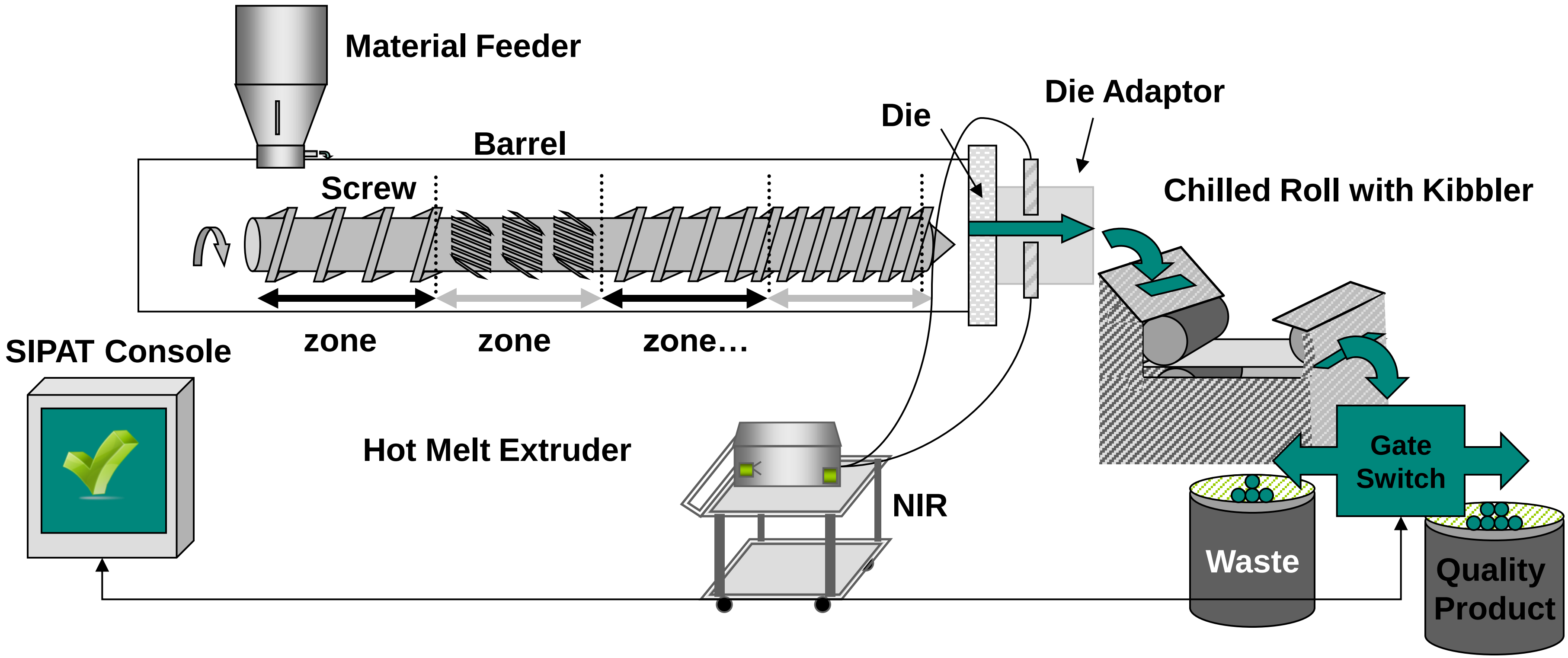
# Use of PAT During Development – RTD Measurement and Scale Independent Responses



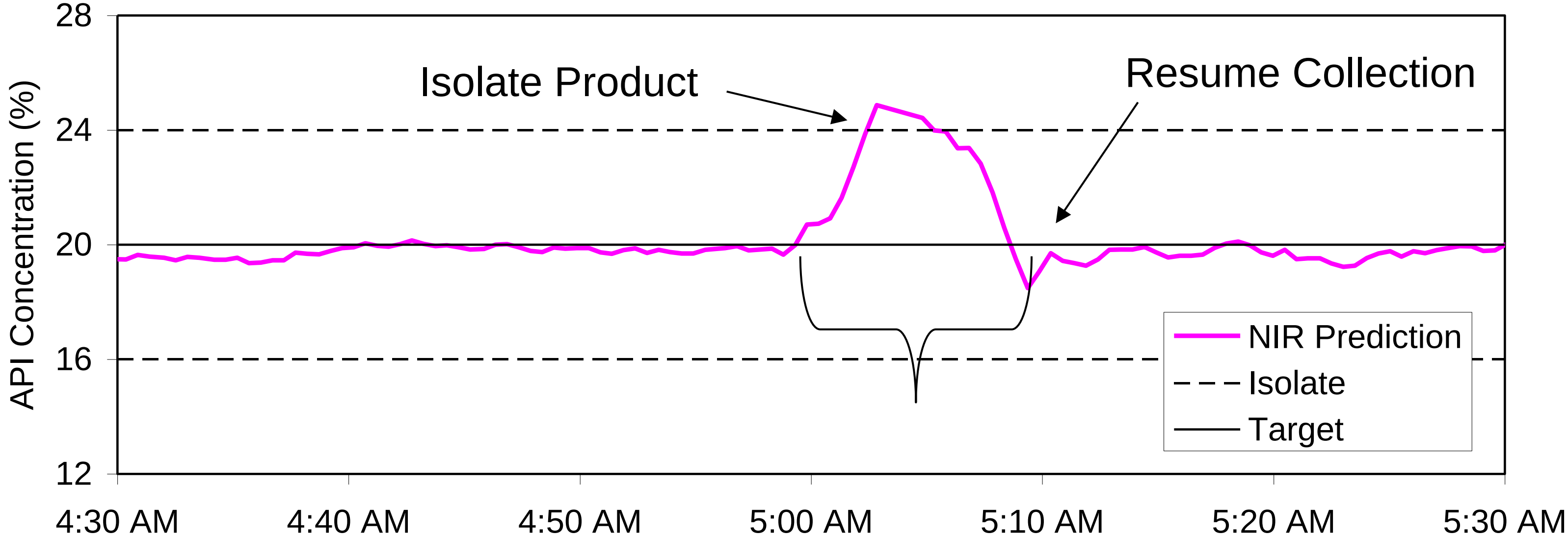
# Use of PAT During Production: Waste Gate Control

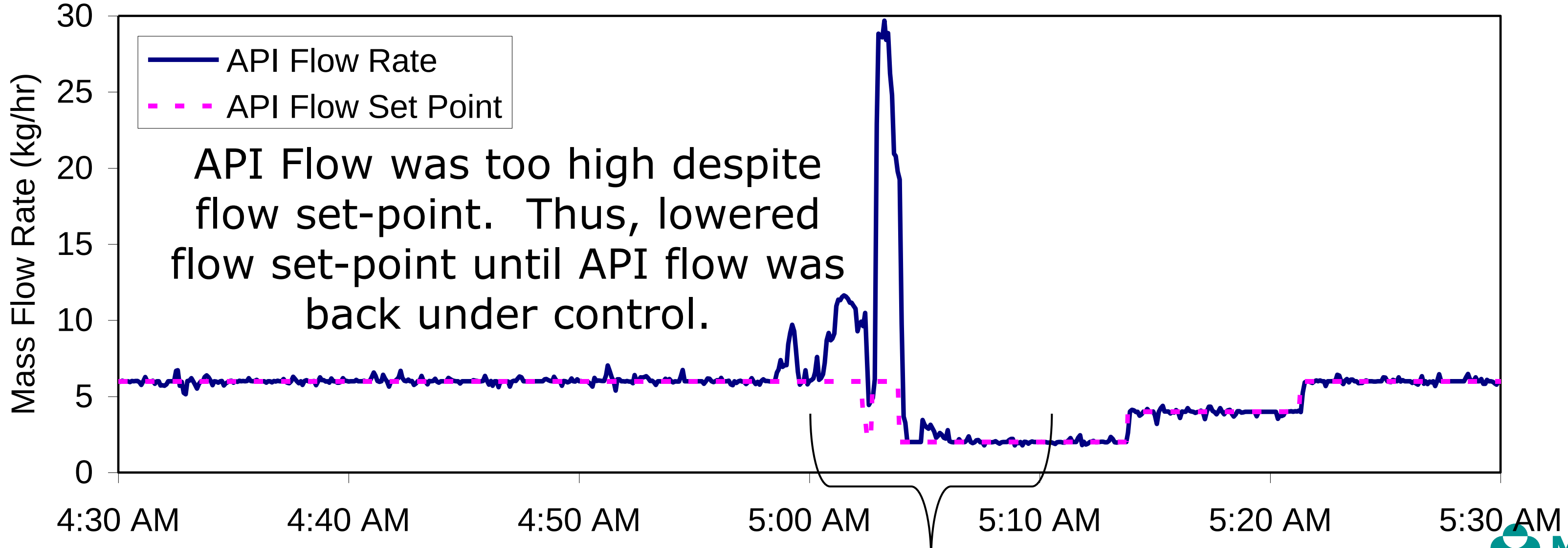
**HME Control Strategy -** PAT control of hot melt extrusion waste gate based upon % drug loading (wt/wt)




- Risk Mitigated
  - Mitigates risks to composite assay and content uniformity failure within the final coated tablets

# Use of PAT During Production: Waste Gate Control




Fault detected and out of spec material diverted to waste

# PAT for HME – Benefits/Drivers

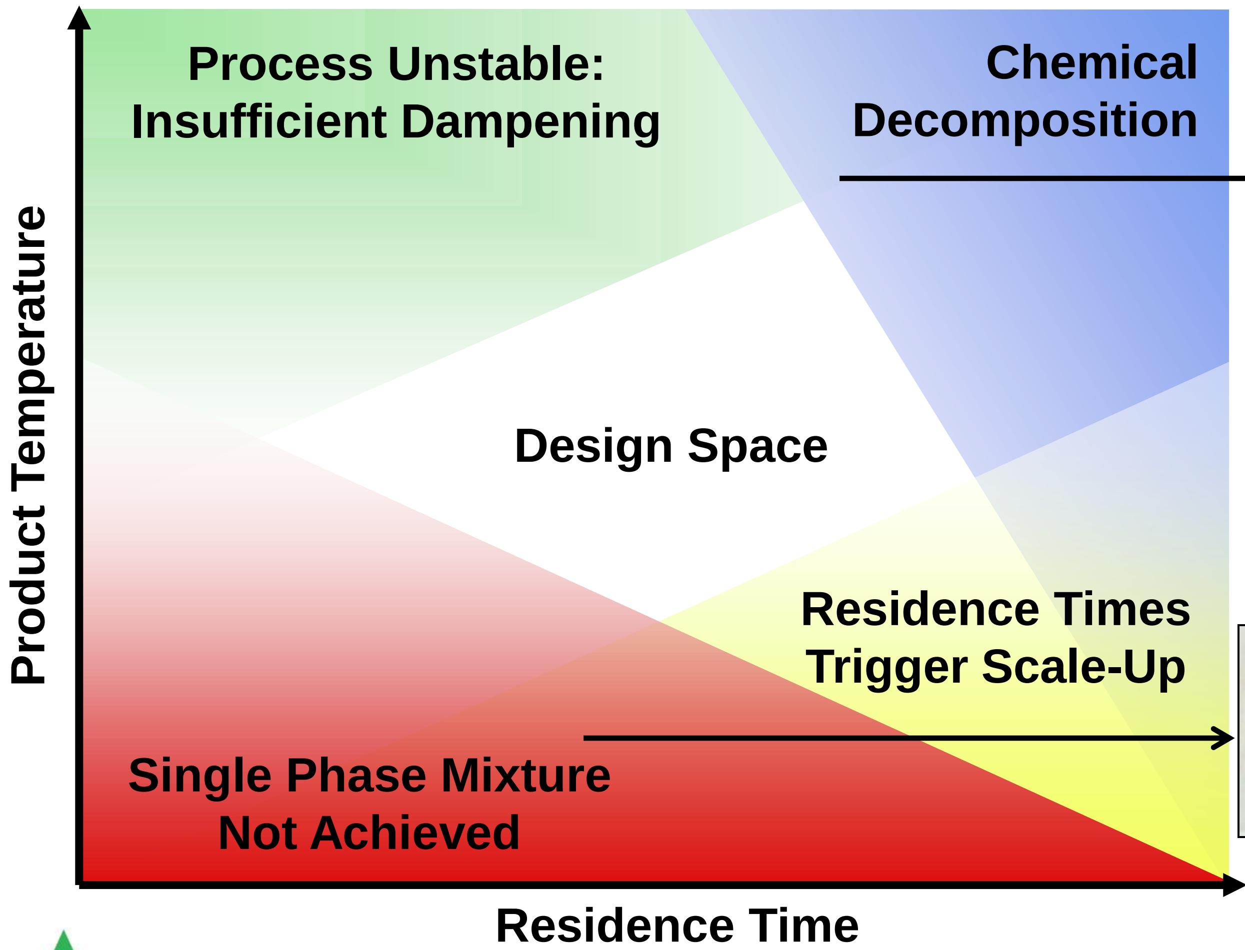
- **Real time quantitative monitoring and detection of process upsets**
  - Verification of composition/uniformity of extrudate
  - Detect pre-mix uniformity, segregation or preferential sticking issues (or other disturbances – feeder noise, process drift, Pressure fluctuations in liquid feeds)
  - Quality control: isolation of off-specification material
- **“Flying Blind” during mass feeder refills**
  - Mass feeders feed at last known conditions during refills
  - Feeders may need to re-tune for raw material lot changes
- **Enhance understanding of process dynamics**
  - Start up/Shut down
  - Time to reach steady state
- **Provide additional information for residence time distribution (RTD)**
  - Help understand process fingerprint and enable scale-up
  - Design process to get desired quality with fixed feeder performance
- **Holistic/Quality by Design approach for quality assurance**
  - Option to include as part of process control strategy
  - Support continued process verification through monitoring

# HME Process Development – Linking Quality to Process

Conceptual Representation of Extrusion Process Space:

$$\uparrow Throughput \ \&or \downarrow Energy = Molecular\ Disperson\ Not\ Achieved$$

$$\uparrow Energy \ \&or \downarrow Throughput = Decomposition$$




# HME Process Development – Linking Quality to Process

### Process Input Parameters

- Barrel/Die/Screw Configuration
- Feed Rate
- Screw Speed
- Barrel Temp Profile

### Scale Independent Response Parameters

- Specific Mechanical Energy
- Residence Time Distribution
- Product Temperature Profile
- Mixing Cycles
- Product Temperature ($T_{melt}$)
- Cooling Rate

### Quality Attributes

- Chemical stability
- Phase/form stability
- Processability
- Moisture content

# Control Strategy Definition for HME

- Option #1: Use of process parameters
  - Scale dependent, proven acceptable ranges easily defined

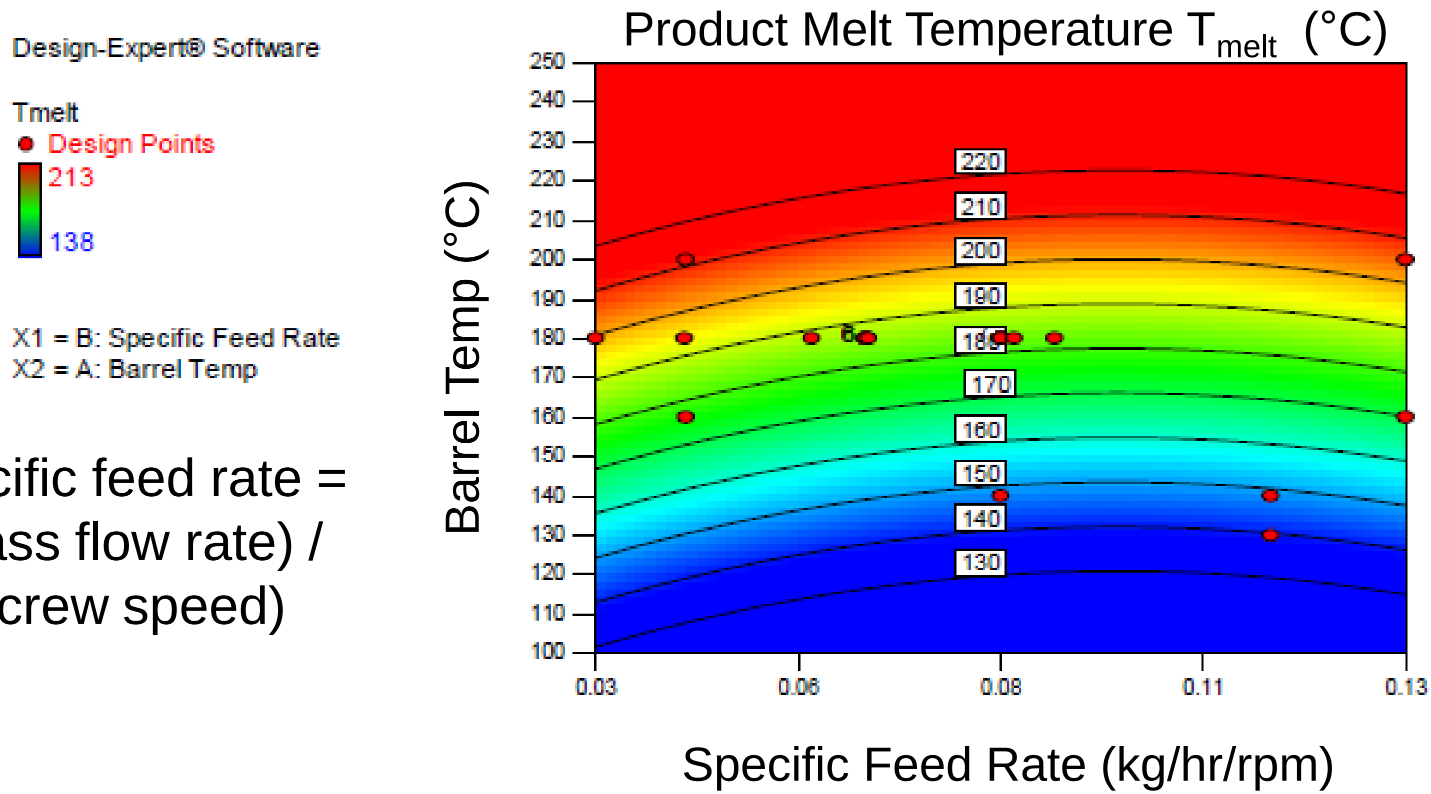
| Unit Operation | In Process Control | Process Parameter Range | Material Attribute | Test Frequency |
|---|---|---|---|---|
| Hot melt extrusion | Screw speed | 150 – 450 rpm | API concentration (20% ±2% wt/wt) | Every batch |
| | Barrel temperature | 140 – 200 °C | | |
| | Material Throughput | 10 – 45 kg/hr | | |

- Option #2: Use of process response(s)
  - Scale independent, design space needs to be established

| Unit Operation | In Process Control | Process Parameter Range | Material Attribute | Test Frequency |
|---|---|---|---|---|
| Hot melt extrusion | Screw speed | Adjust material throughput, barrel temperature, and screw speed to meet melt temperature and NIRS API concentration measurement | Melt temperature $138 \leq T_{melt} \leq 213°C$ | Every batch |
| | Barrel temperature | | <u>and</u> | |
| | Material Throughput | | API concentration (20% ±2% wt/wt) | Every batch |

# HME Process Development – Relationship Between Parameters & Reponses

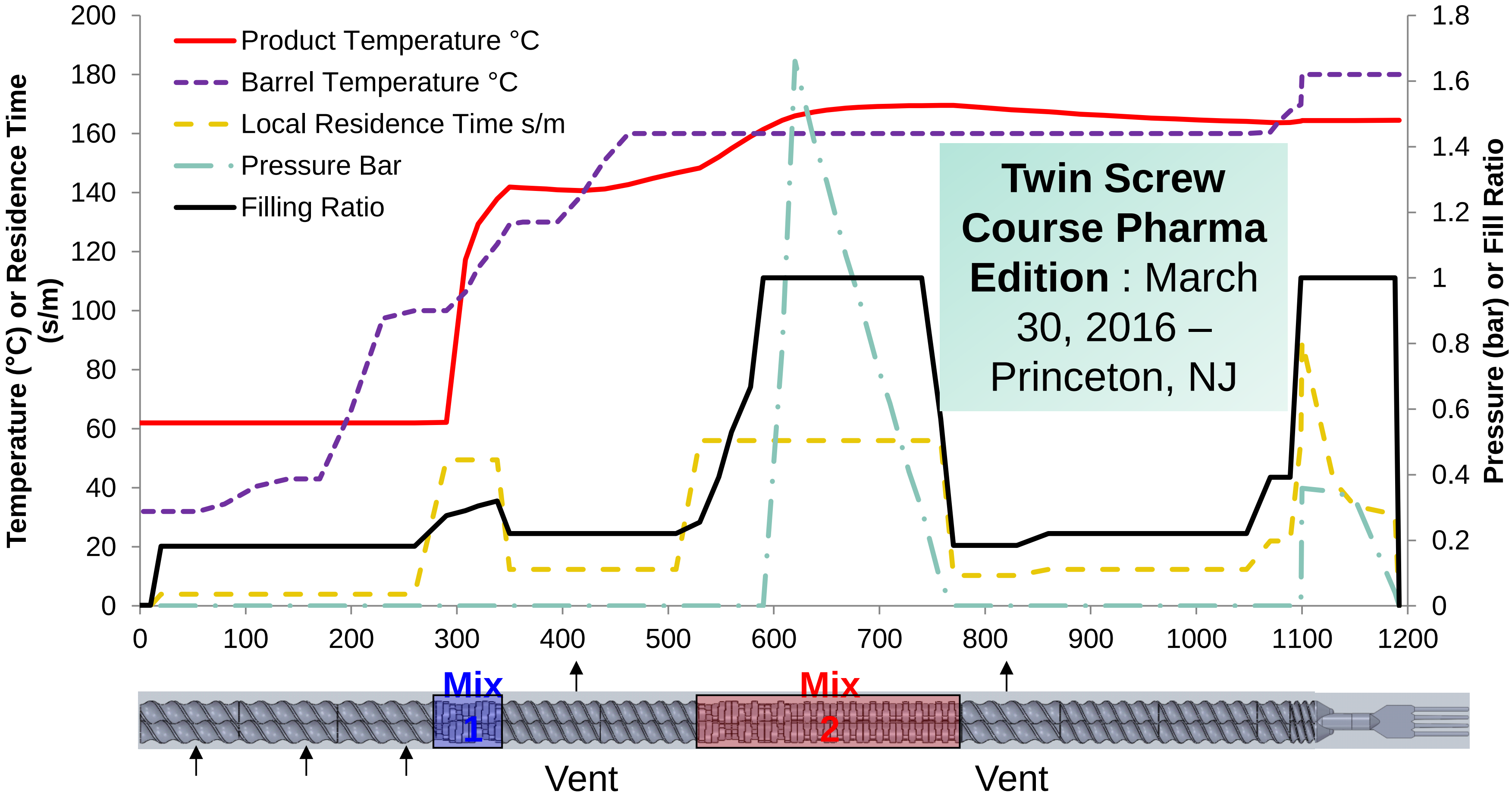
- $T_{melt} = f$ (barrel temperature, screw speed, feed rate, screw design, die)




Specific feed rate = (mass flow rate) / (screw speed)

- $T_{melt}$ is only a function of barrel temperature, screw speed, and feed rate once screw design & die type are selected for the process
- Represents design space and translates product attribute back to process parameters

# HME Process Development: Modeling of HME via SCC's Ludovic



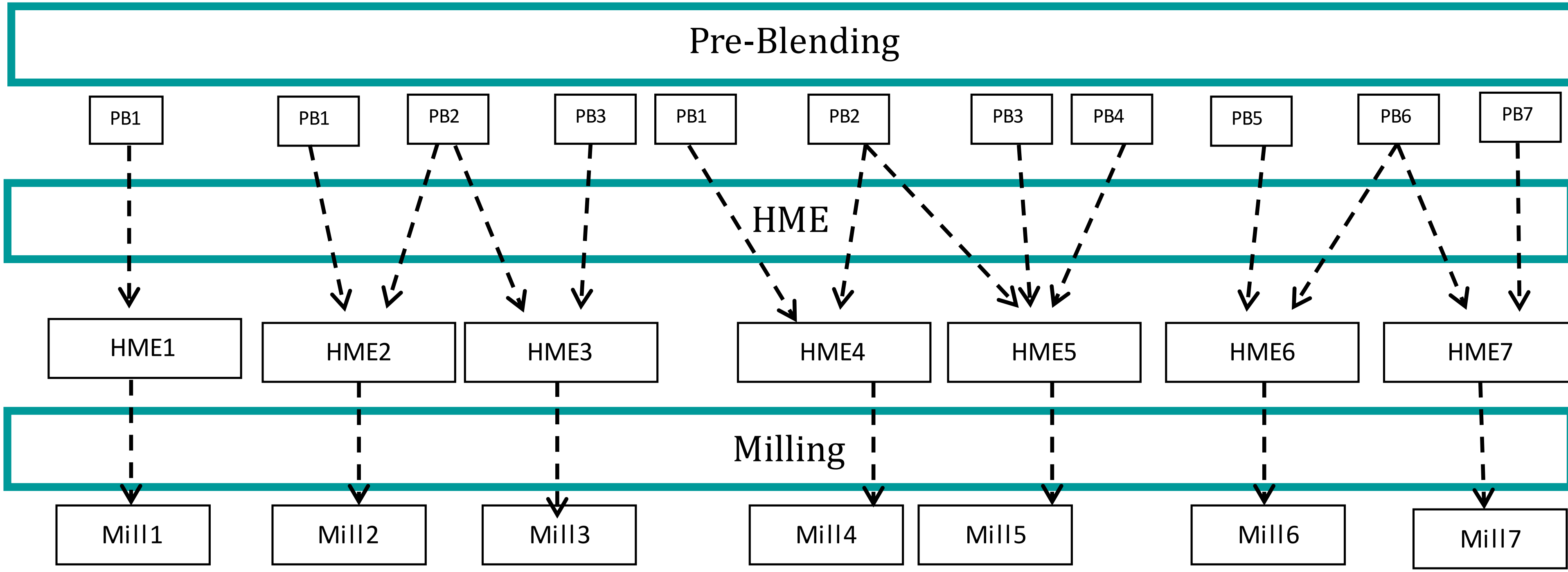

- 1D HME process simulation at 27mm scale, 24kg/hr and 380rpm using Ludovic
  - product temperature changes with screw axial position
  - majority of residence time is spent in the fully filled mixing (kneading block) sections
- Modeling moves us from measuring only inlet and outlet to process understanding

# Batch Size Definition for HME

- Batch size definition could be based on upstream or downstream processing depending on limiting factor(s)
- Individual feed processing will be based on downstream limitations
- Using pre-blends, an extrusion batch can be 1 pre-blend or multiple pre-blends (same process, same control strategy)
- DOM in all cases is the first addition of API to the “batch” – i.e. if 7 pre-blends = 1 HME batch, DOM = API addition to pre-blend #1

# Batch Size Definition for HME - Example

- Pre-blending = 365 kg in an 1800 L tote (based on pre-blend bulk density)
- HME = 1-X pre-blends - extruded, kibbled, & vacuum transferred to 1800 L totes
- Milling = ≤ 650-675 kg in an 1800 L tote (based on kibbled HME bulk density)



# Conclusions

- Hot melt extrusion has been utilized for continuous mixing for many years
  - Extent of CP utilized should be balance of technical risks and business benefits
- Enhanced process understanding obtained through QbD development enables attribute based design space
  - First-principles and statistical process modeling contributes to this understanding
- PAT such as in-line transmission NIR leads to stronger process development and process control
- Time interval between new technology lab installation and approved products often takes a decade or more
  - Teams like FDA's Emerging Technology Team and MHRA's Innovation Office have the opportunity to reduce this cycle time

# Acknowledgements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- Hot Melt Extrusion Technology Development Team
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