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Hot melt extrusion and continuous wet granulation in the pharmaceutical industry

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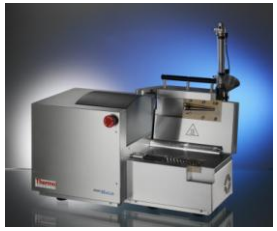
Topics

- Requirements for small scale extrusion/compounding systems
- Laboratory extruder systems
- Laboratory test specimen preparation
- Characterisation techniques
  - Thermal
  - Rheological
  - Spectroscopic
- Pharmaceutical holt melt extrusion (HME) and case studies
- Pharmaceutical wet granulation with twin screw extruders

Requirements for small scale extrusion systems

- Scientists need to do more with less!
  - e.g. Limited by availability and/or cost or raw materials
- Small scale materials should be representative of what can be produced on a larger scale
- Screening of large numbers of formulations requires easy/rapid cleaning of equipment
- Trouble free scale-up to manufacturing scale

Twin Screw extruder portfolio

Mini	11 mm	16 mm	24 mm	36 mm
 MiniCTW	 Process 11	 EuroLab		
 MiniLab		 EuroLab Pharma		
 Pharma Mini	 Pharma 11	 Pharma 16	 Pharma 24	 Pharma 36

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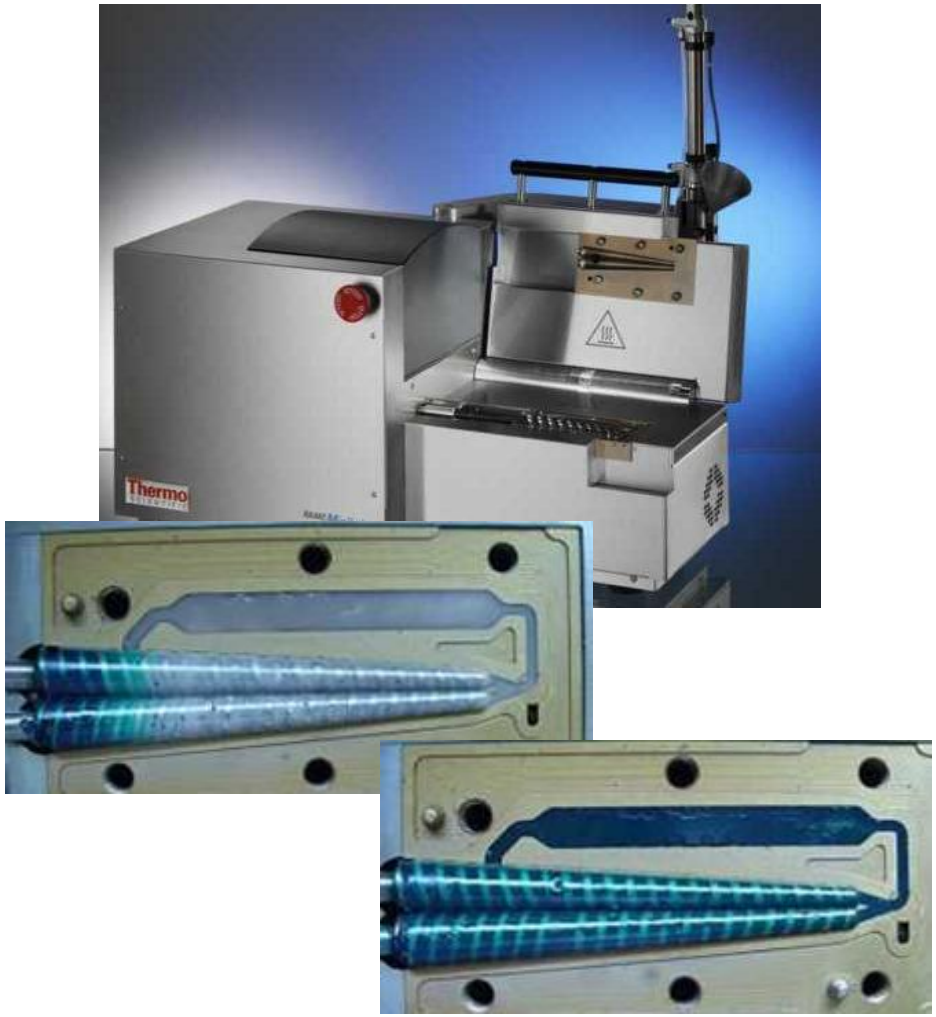
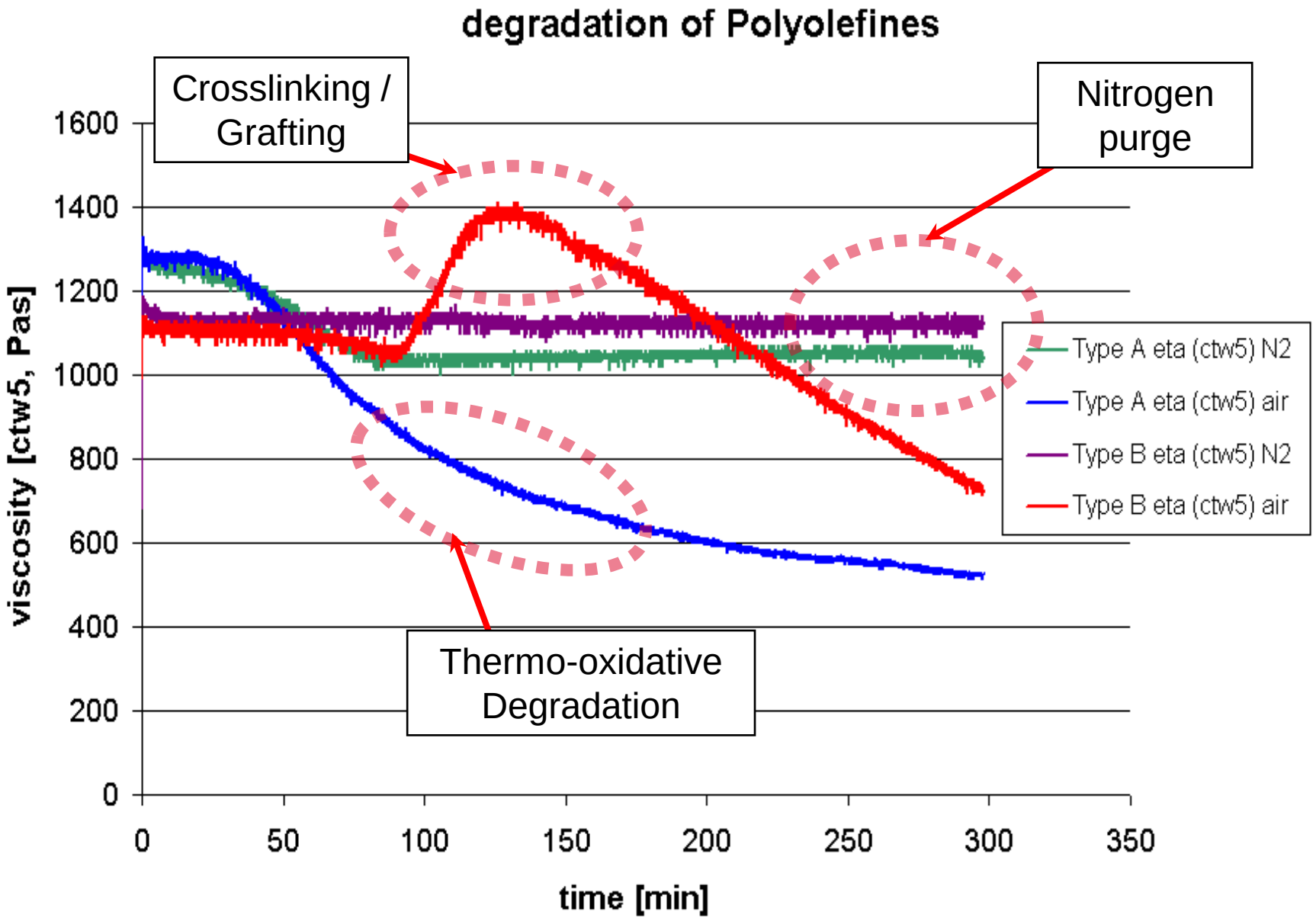
Lab extruder systems

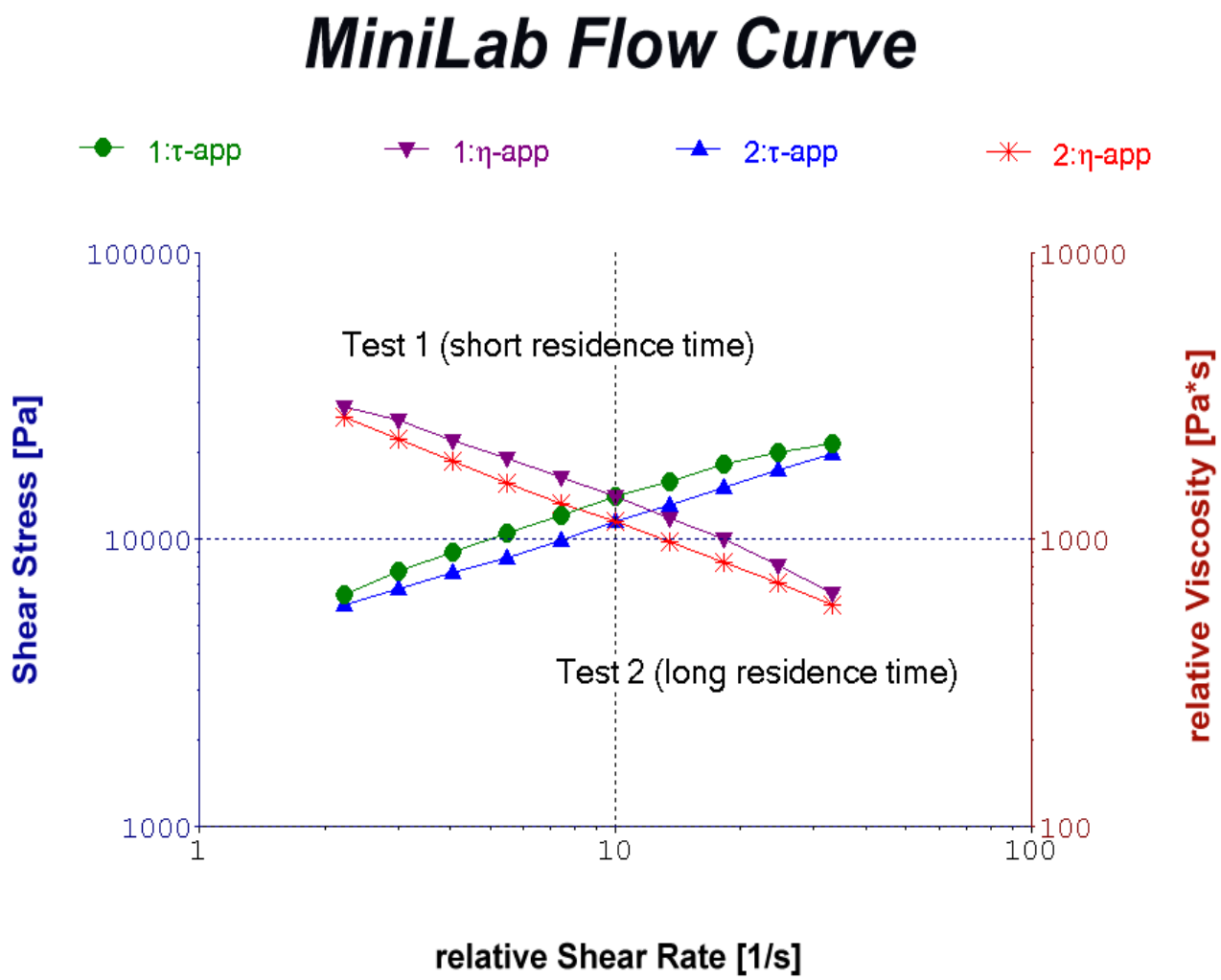
Miniature conical twin screw extruder/mixer

- Small sample size (min 3g) minimises material requirement/cost
- Clam-shell barrel increases ease of cleaning
- Back-flow channel provides mixing capability with minimum material usage
- Capillary Rheology measurements
- Interchangeable screw configuration for optimisation of shear regime
- Feeding options allow working with powder and pellets




degradation of Polyolefines
Crosslinking / Grafting
Nitrogen purge
Thermo-oxidative Degradation
viscosity [ctw5, Pas]
time [min]
0
200
400
600
800
1000
1200
1400
1600
0
50
100
150
200
250
300
350
Type A eta (ctw5) N2
Type A eta (ctw5) air
Type B eta (ctw5) N2
Type B eta (ctw5) air

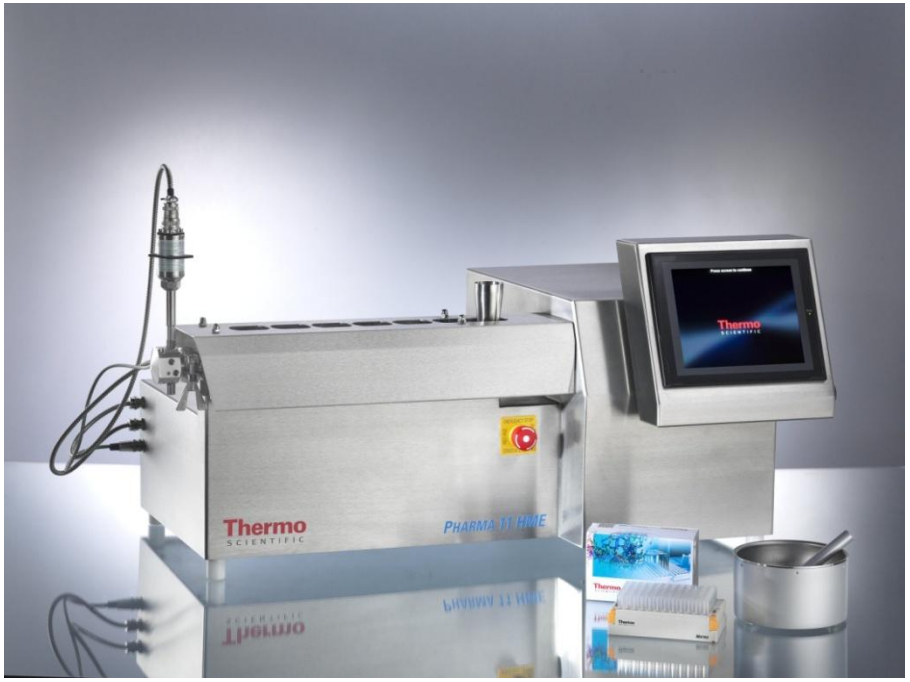
MiniLab - Relative Rheology (PP at 220°C):



Lab extruder systems

Twin screw compounder

- Small sample size (min 20g) minimises material requirement/cost
- Continuous output up to 2Kg/hour
- Fully removable top-barrel increases ease of cleaning
- Fully modular screw configuration for optimisation of shear/mixing regime
- Feeding options allow working with powder, pellets, liquids and split feeding
- Directly scalable to larger machines



Small…

…Simple…

…Scalable

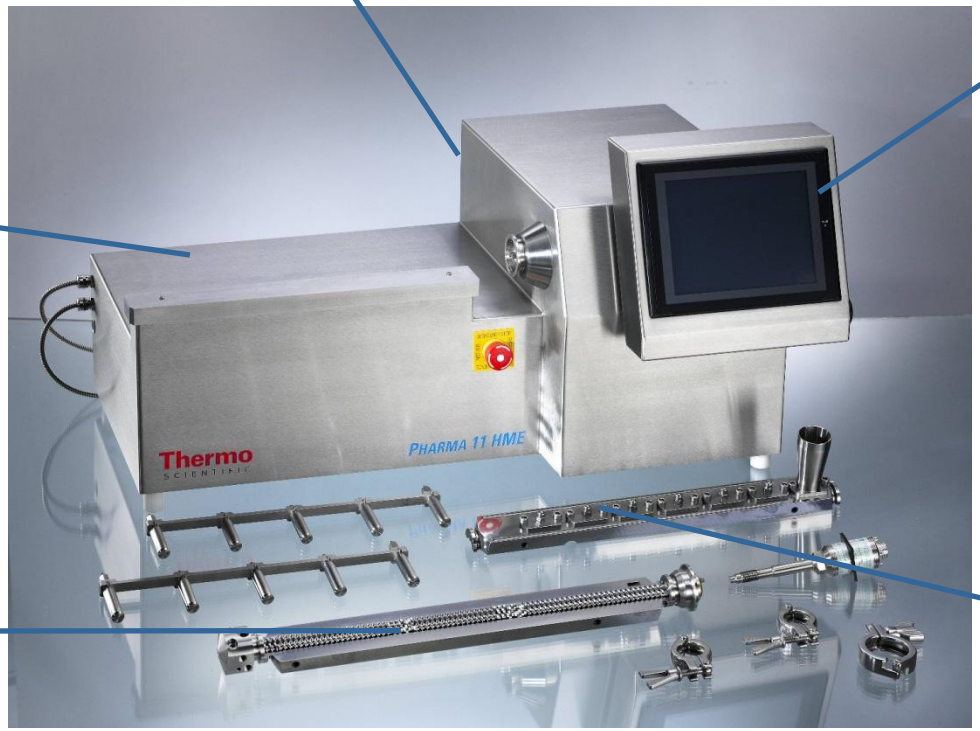
Lab extruder systems

Twin screw compounder for Pharma

Monocoque design; fan less without air ventilation

Touch screen control with password protection

Small footprint bench top design with integrated electronics



Segmented screw design

Removable and exchangeable product contact parts

Scalability

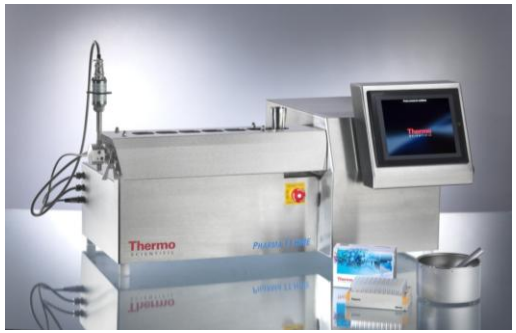
Aim: transfer knowledge obtained in the lab directly to production

- Material “experience” within process should be the same
- Assumption: “Similar” geometry in lab and production
  - $L/D = const.$ very obvious
  - $D_o/D_i = const.$ also obvious, but not the case for all manufacturers
  - $c_s/D = const.$ to obtain same shear rate at same screw speed

- Same barrel & die temperatures
- Same screw speed and configuration
- Simple throughput scale up by: $\dot{m}_P = \left(\frac{D_P}{D_L}\right)^3 \cdot \dot{m}_L$ W. Schuler/ 1996
- Residence time and Melt temperature should be the same
- Specific Energy should be const. $e = \frac{P_m}{\dot{m}} = \frac{2 \cdot \pi \cdot n \cdot M \cdot 60}{\dot{m}}$ (by adjusting throughput)

Scale-Up: Standardised parameters

- Consistency of key geometries across our extruder family provides for easy scale-up from lab to production:



11mm

20g->2Kg/hr

16mm

5Kg/hr

24mm

25Kg/hr

Lab scale test specimen preparation

Injection moulding system

- For preparation of representative test specimens
- Small sample quantity requirements @1g or less
- Variety of test piece moulds for thermal, mechanical and rheological testing
  - Bars,
  - Disks
  - Dogbones
  - Tablets

Material characterisation techniques

- Thermal Analysis
  - Tg
  - Mpt
  - Curing
  - Composition
- Rheological
  - Flow properties vs. shear rate / temperature
  - Tg
  - Curing
- Spectroscopic \ microscopic
  - Chemical composition
  - Structural (polymorphism)
  - Spatial mapping / dispersion uniformity

Pharmaceutical Hot Melt Extrusion

- Why use Hot Melt Extrusion technology?
  - different applications: sustained release, solubility enhancement, taste masking
  - anhydrous process, no solvents
  - simple process (limited number of process steps, single step?)
  - short residence time
  - different dosage forms (depending on shape of the die and downstream processing equipment): tablets, granules, pellets, films, ...
  - continuous process (high throughput)
  - in-line monitoring possibilities – PAT / QBD
  - co-extrusion (e.g. manufacturing of high-precision medical devices)

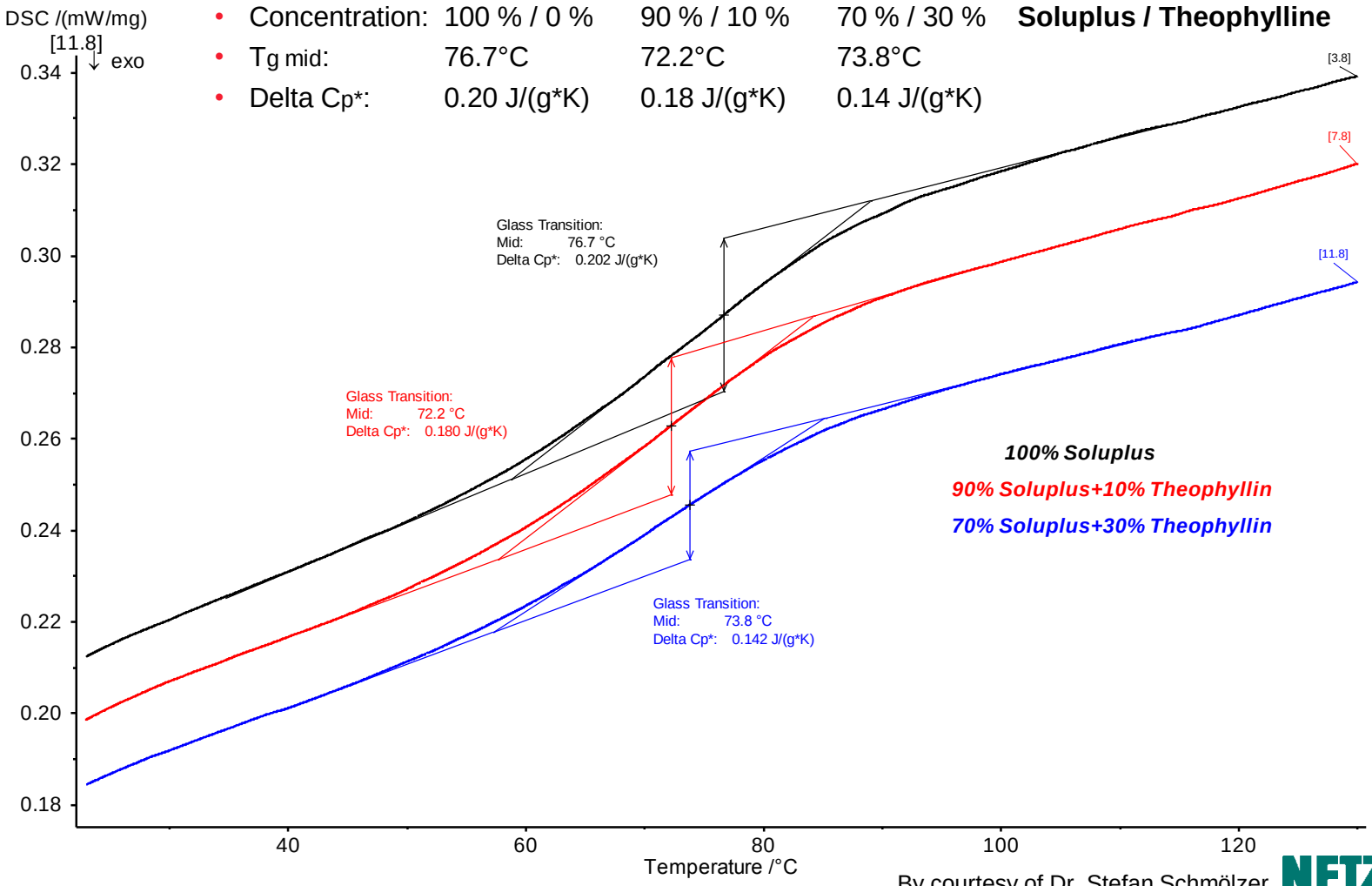
Hot melt extrusion 1

- Studying interaction of API and polymer
- Small mixes made with micro compounder
- Tg change studied with DSC and Rheology
- API may act as plasticiser if compatible

DSC measurement

- 2nd heating run (no residual strains) with 10 K/min

• Concentration:	100 % / 0 %	90 % / 10 %	70 % / 30 %	**Soluplus / Theophylline**
• Tg mid:	76.7°C	72.2°C	73.8°C	
• Delta Cp*:	0.20 J/(g*K)	0.18 J/(g*K)	0.14 J/(g*K)	



By courtesy of Dr. Stefan Schmölzer

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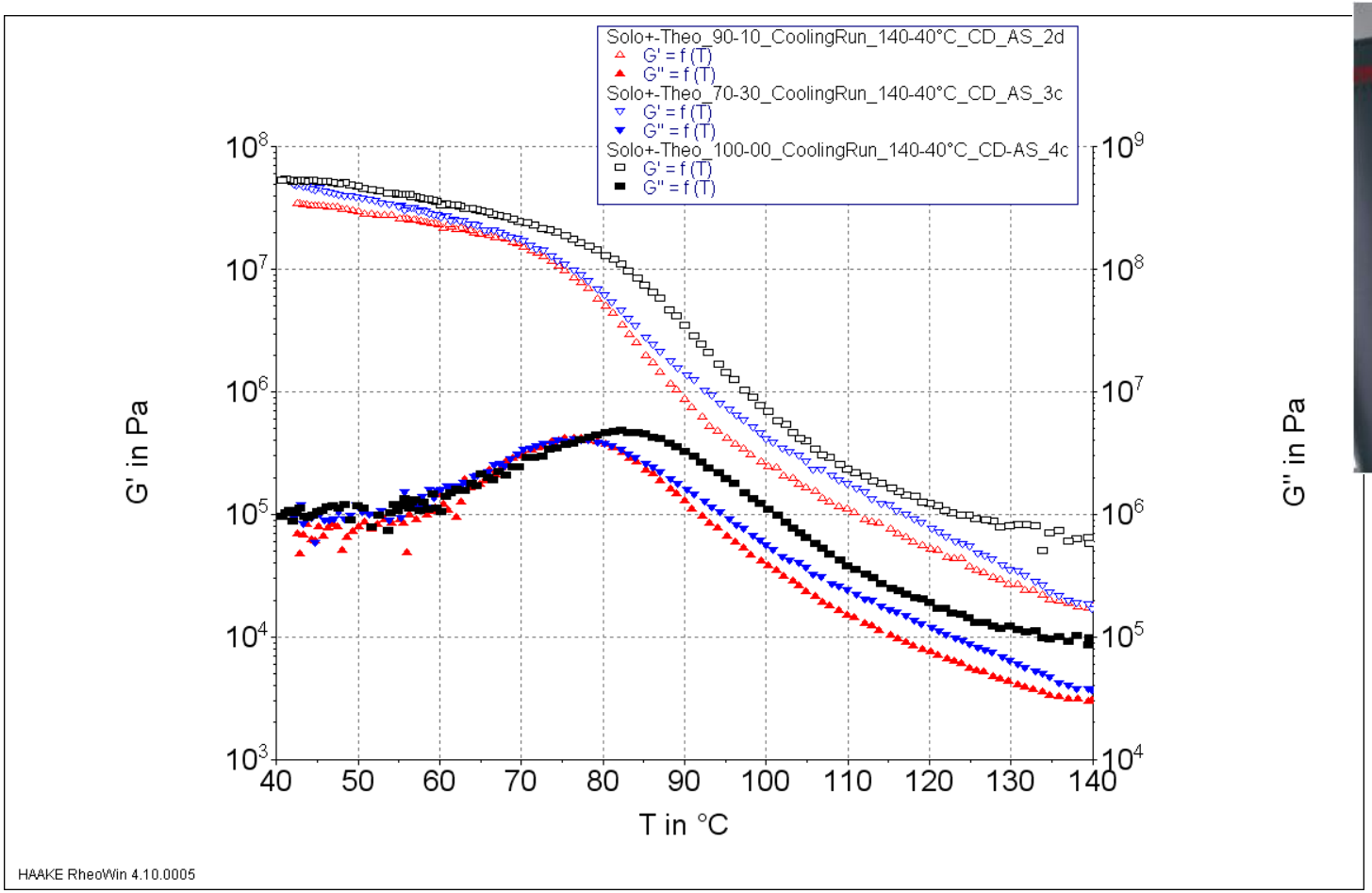
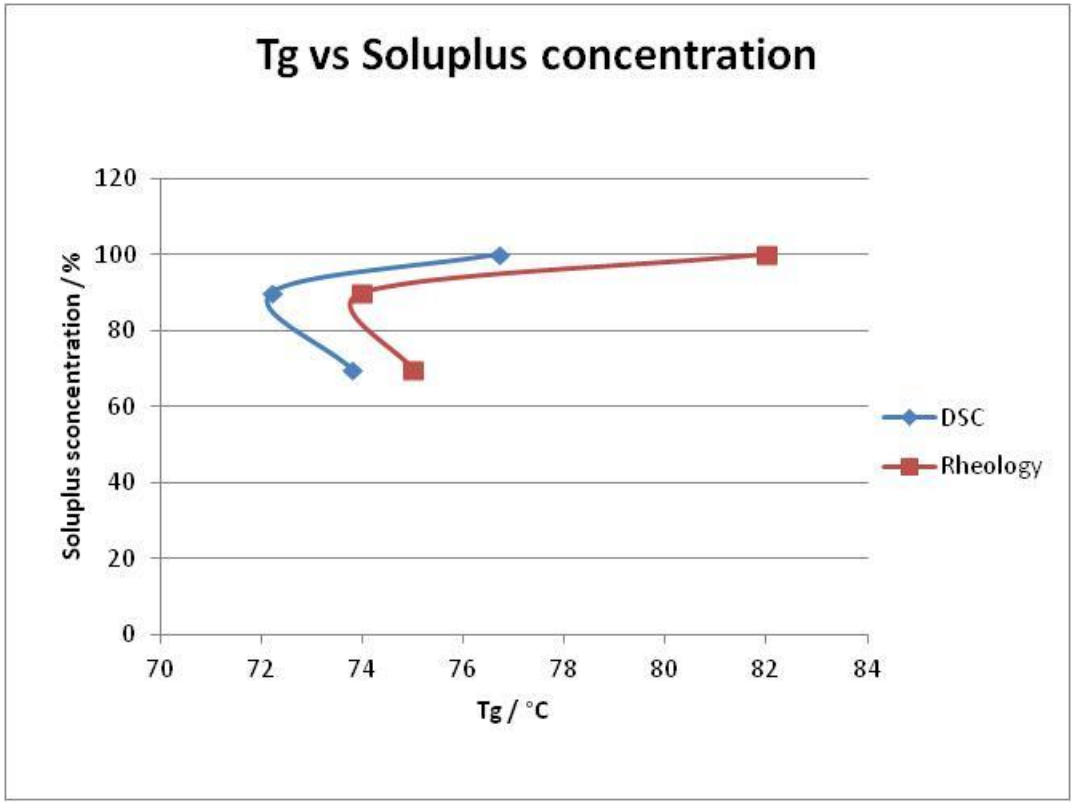
Viscosity/modulus measurement
Plate/plate measuring geometry

- Plasticizer effect of API on Tg – Cooling run (5 K/min)



Hot melt extrusion

- Tg lowering indicated API is acting as a plasticiser – compatible?
- Non-linear Tg/concentration response- indicative of solubility limit of API in polymer system?



Hot melt extrusion 2

- Preparation of realistic dosage form from small samples
  - To demonstrate feasibility of analysing the characteristics of a solid dispersion of a potential final dosage form prepared from a small sample size
  - Can small-scale samples be representative of what will be produced at a larger scale?
  - Can representative dosage forms be produced from minimal amounts of raw materials ? eg a tablet/capsule

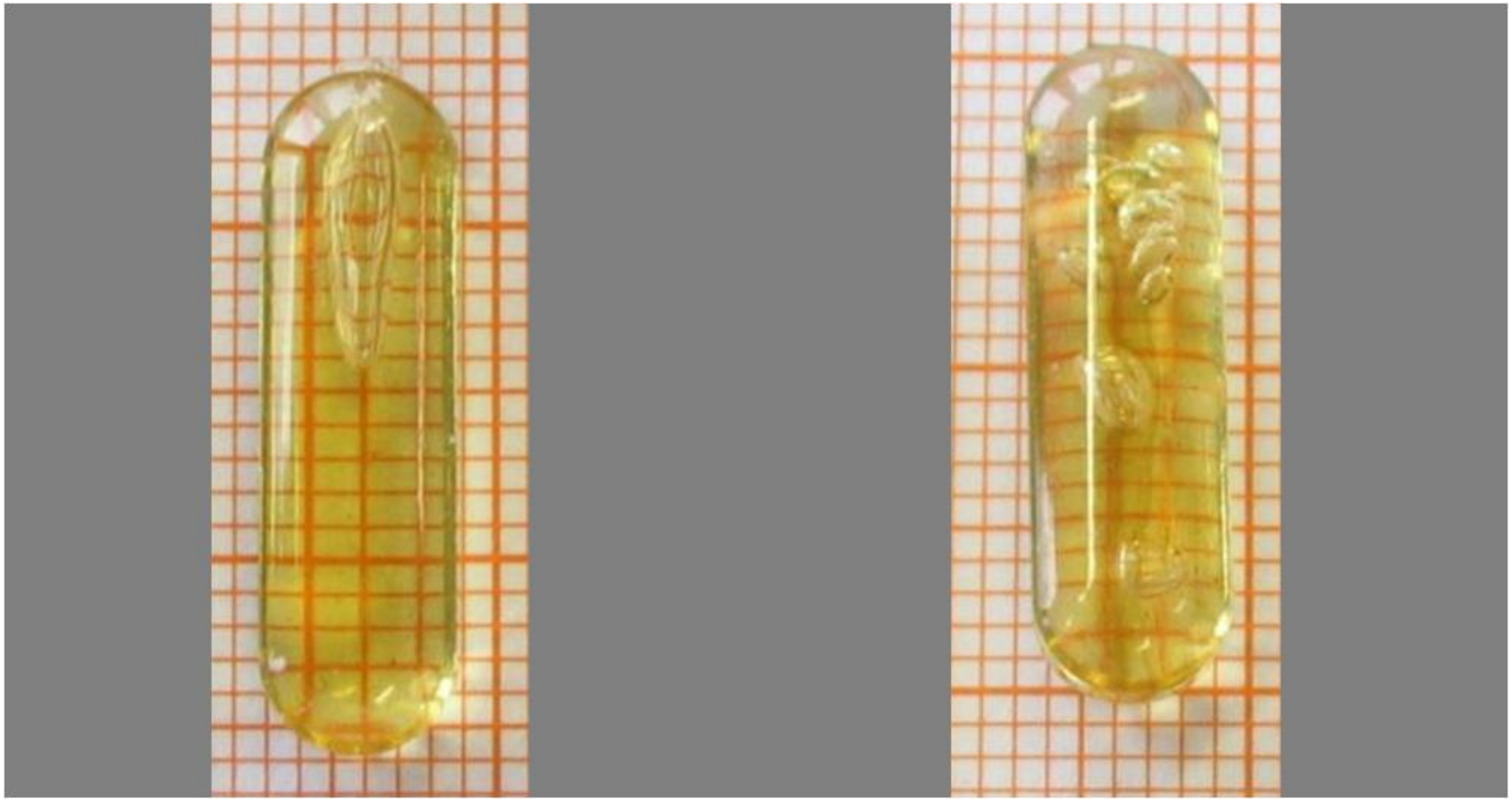
Hot melt extrusion

- Sample preparation
  - A physical blend containing 15% itraconazole and 85% Soluplus® was prepared by shaking in a PE-bag for 3 minutes.
  - The blend was then melt extruded in a conical small scale extruder (Thermo Fisher PharmaMiniHME) with 150 rpm at 170°C.
  - The extruder was feeding the melt directly into the reservoir of the Thermo Fisher Minijet injection moulding device.
  - Oblong shaped tablets of a dimension of 20 x 6mm were prepared by injection moulding.
  - The powder blend was fed manually into the reservoir of the Minijet without having it melt extruded and tablets moulded as above.
  - Other samples were also extruded and pelletised from 3mm diameter strands, but not injection moulded into tablets

Results

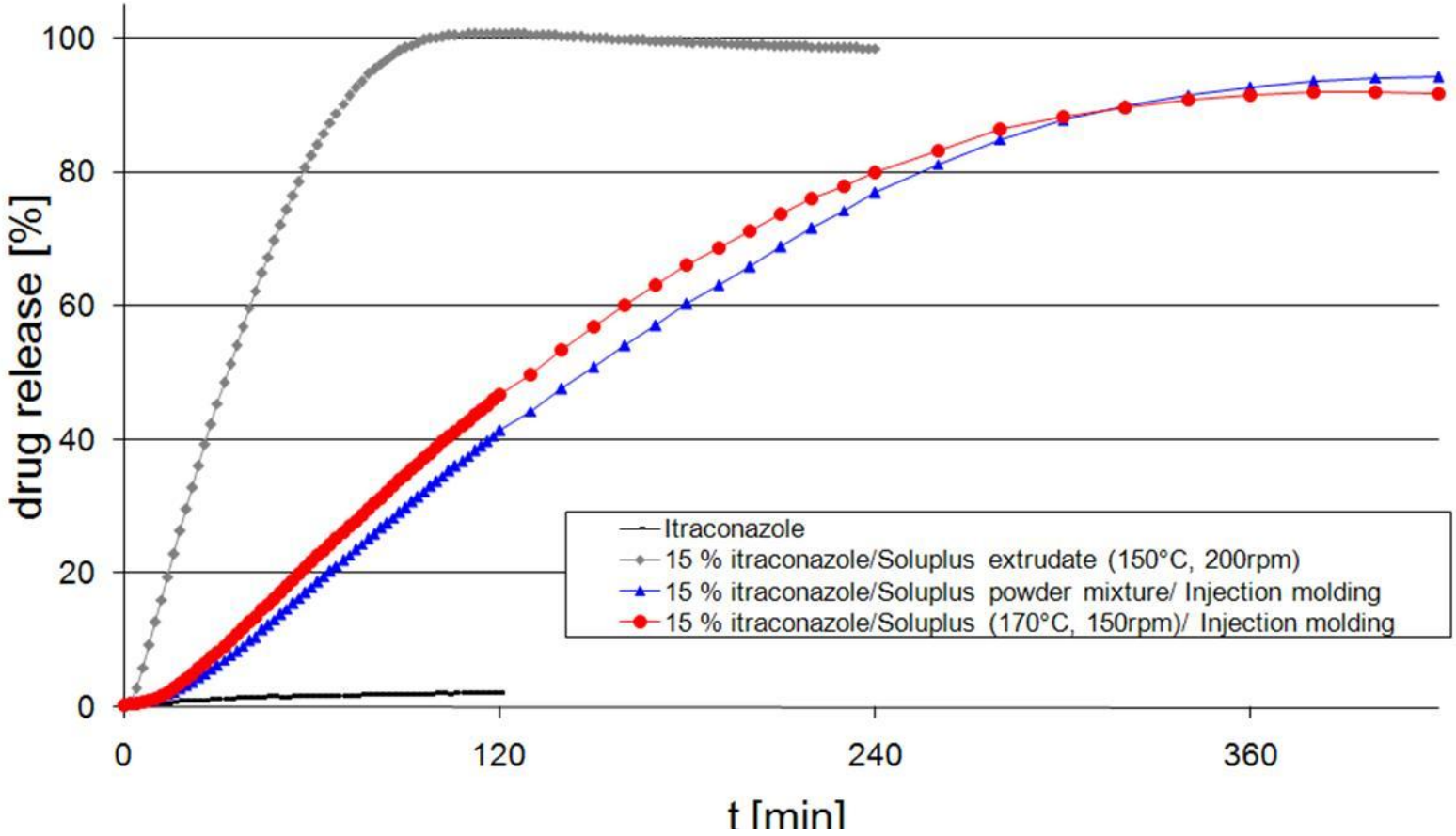
Tablet from extrudate

Tablet from blend



Results

Drug release tested on melt extrudate granules, on injection moulded tablets and on pure itraconazole



Granulation

- **Wet granulation** involves the agglomeration of a mix of dry primary powder particles using a granulating fluid.
- The fluid, which is added during the granulation step, must be pharmaceutically safe and volatile enough so that it can be evaporated by a subsequent drying step.

- In **Melt granulation** the binding fluid is created by heating the formulation and causing one or more of the dry ingredients to become molten. Cooling the mix at the end of the granulation step solidifies the molten binder.

Reasons for Granulation

- To prevent segregation of the constituents of the powder mix
- Aid downstream processing by improving the physical characteristics of the mix in terms of:
    - Flow
    - Density
    - Dustiness
    - Compressibility

Pharmaceutical Batch Granulation

- Traditional batch processes
  - High speed wet granulation (like APV, GEA, Fielder.)
  - Roll Compaction
  - Fluidised bed granulation
- Risks of Batch to batch variation require careful and complex procedures and controls.
  - Method and order of charging ingredients
  - Time and technique for introduction of binders
  - Definition of end point
- Large scale equipment needed in development to reduce risk of scale-up.
- Large quantities of expensive API required
- Difficulty to produce small samples on production scale equipment.

Continuous Granulation

- Controlled continuous process
  - *Suitable for PAT*
  - *No "batch to batch" variation*
- Small inventory of "in-process" materials
  - *Reduced risk of product loss*
  - *Reduced Powder risks*
- On demand production
  - *Reduced scale-up risk*

Motivation for adopting continuous granulation

- **Financial and business drivers**
- Reduced footprint
  - facilities cost
- No or little scale up from development to commercial
  - reduced tech transfer costs and risks
  - reduction in API requirements through development
- Potential for common platform throughout development and commercial network
- Reduced capital and OPEX costs
- Lights out operation
- Containment of high actives
- Potential for modular construction approach
- Reduced inventory – scope for just in time delivery

- **Technical Drivers**
- Implementation of PAT
- Scope for improved control and consistency

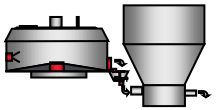
Source ISPE Conference
John Robertson GlaxoSmithKline

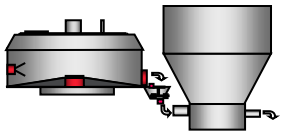
Batch vs. Continuous Granulation

3-10 litre

Phase 1

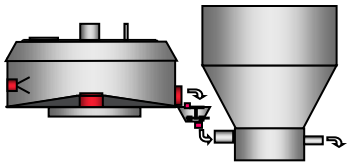
65-150 litre

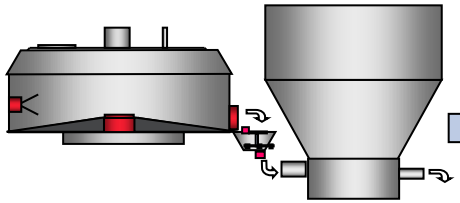




Phase 2

300-600 litre





Phase 3

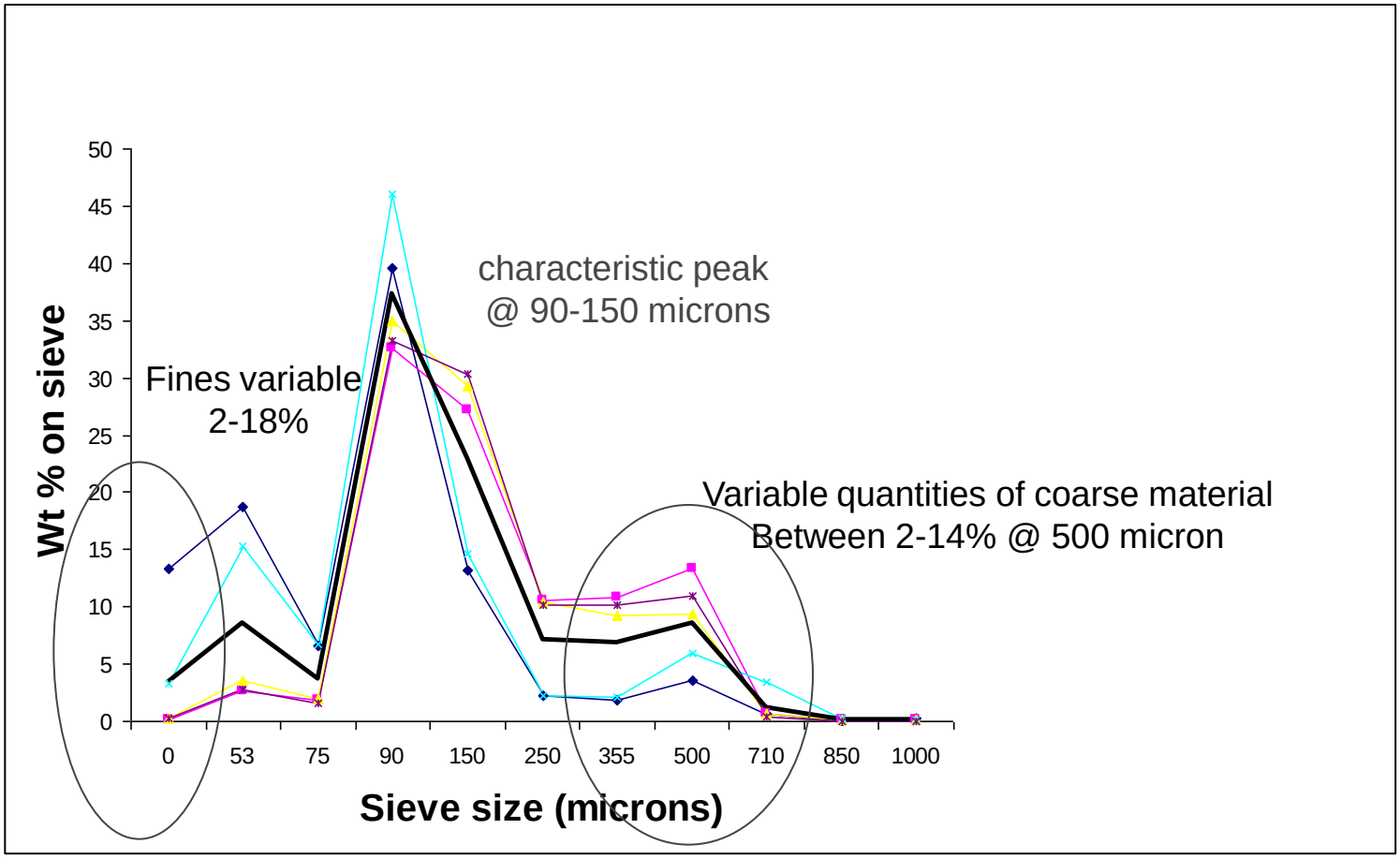
Pharmalab 16mm

Phase 1

Pharmalab 24mm

Phase 2 **and** Phase 3

Comparison of materials – example of batch mixed granules



Source ISPE Conference
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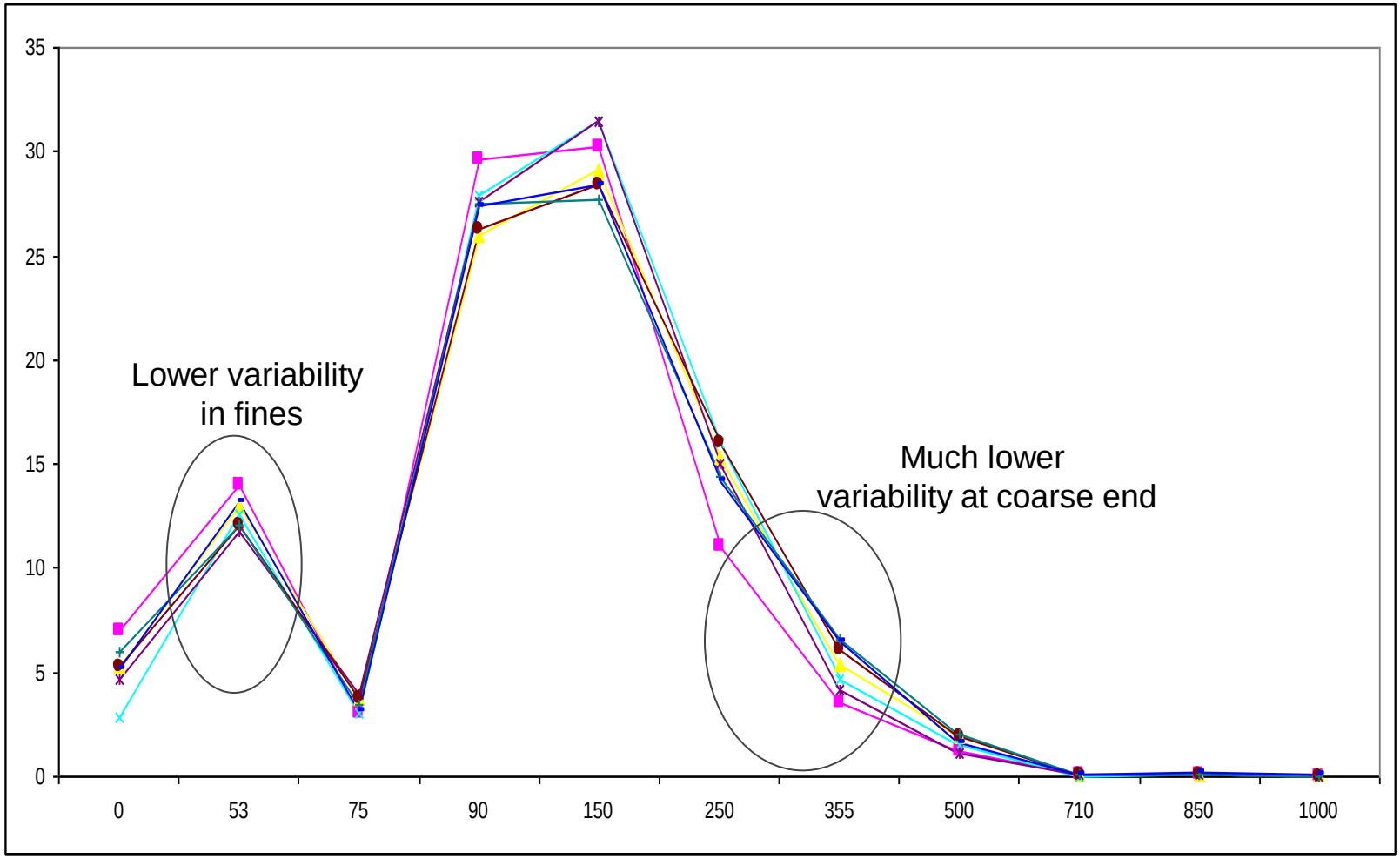
Comparison of materials – example of TSG granules



Potential for more consistent process !

Source ISPE Conference
John Robertson GlaxoSmithkline

Twin Screw Solutions for TSG

11 mm	16 mm	24 mm	36 mm

EuroLab Pharma

Pharma 11

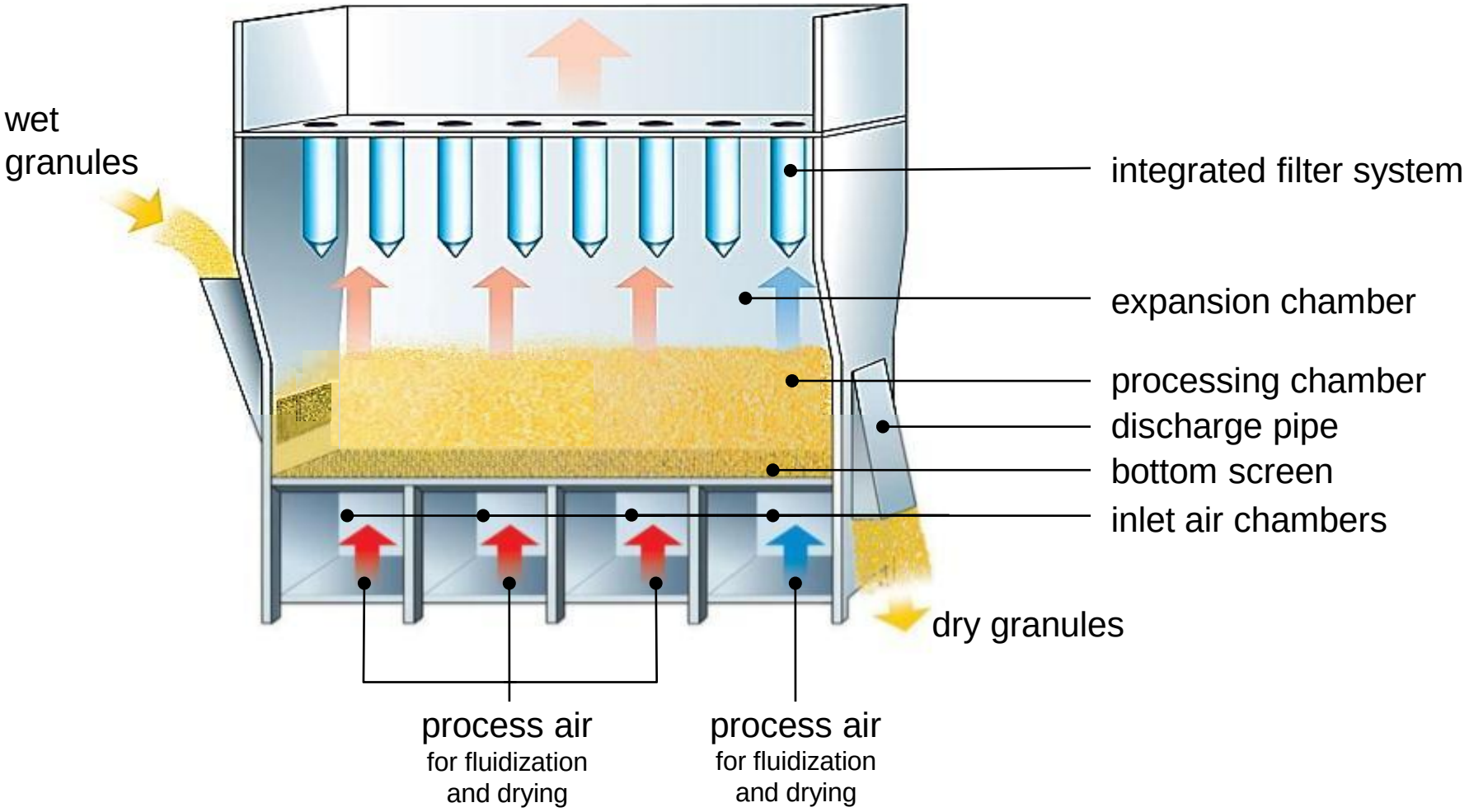
Pharma 16

Pharma 24

Pharma 36

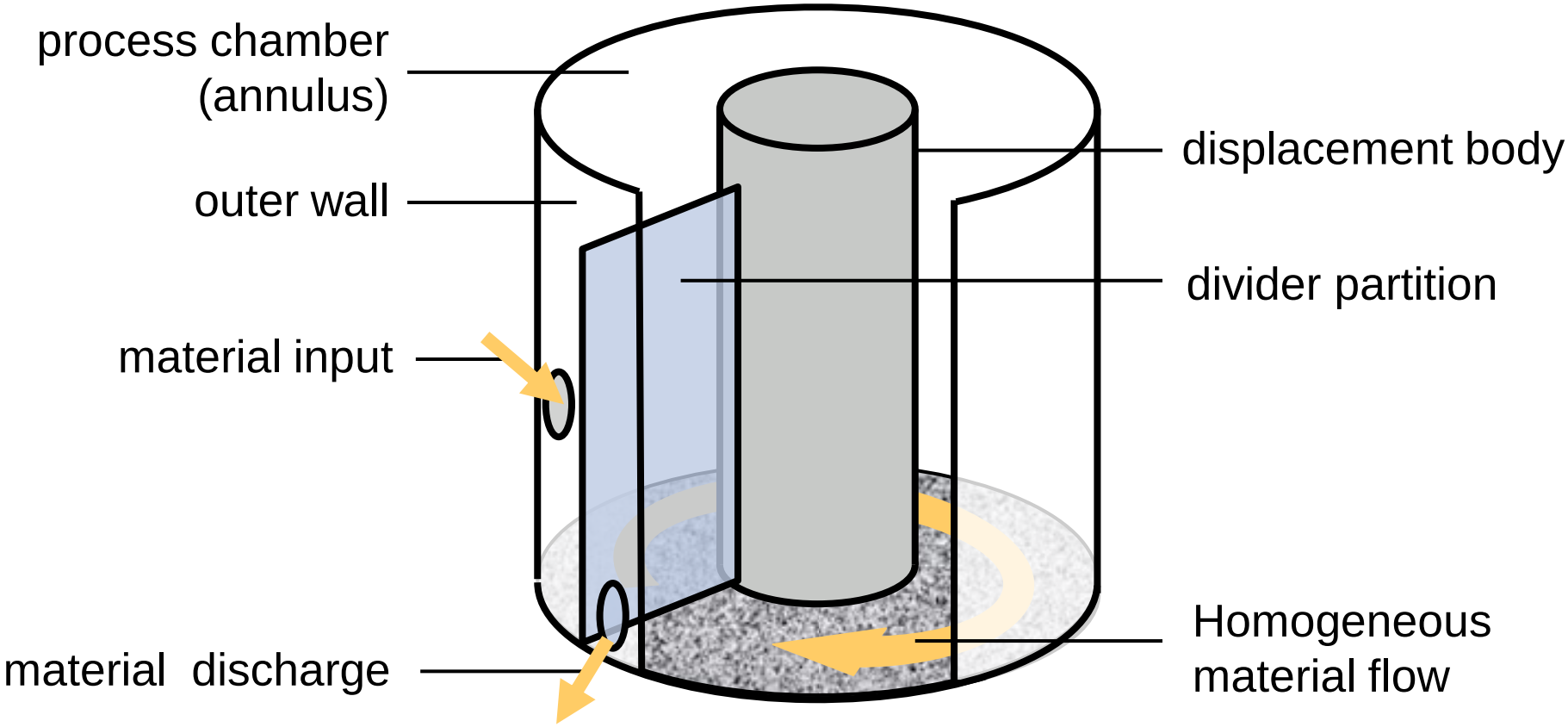
Continuous Fluid Bed Drying

- Principle theory of continuous fluid bed drying



Continuous Fluid Bed Drying

- Principle GF5: ring-shaped process chamber



Continuous Fluid Bed Drying

- Process development with GPCG 2 LabSystem

Process overview

- Batch drying
- Top spray granulation
- Wurster coating
- CPS Pelletization
- Rotor Pelletization
- NEU: Continuous Drying

Conclusions

- Continuous manufacturing is becoming increasingly important in the pharmaceutical industry
- HME opens up new formulation opportunities for drug delivery
- Continuous granulation provides a real alternative to traditional batch manufacturing
- A number of tools are available for early stage studies right up to manufacturing

Thankyou ☺