Continuous Granulation using Twin Screw Extruders

A modular approach to increase your yield in pharmaceutical production.

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Combine Expertise for your success

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- $ 10+ billions in revenue
- 37.000 employees
- 350.000 customers

- Establishing extrusion technologies in thepharmaceutical industry
  - Hot Melt Extrusion
  - Wet Granulation

Glatt®

- Glatt group 1.500+ employees
- represented in 20+ companies worldwide

- Market leader in integrated process solutions for solid dosage forms
  - Drying
  - Granulation
  - Coating

One stop shop for tablet production

Content

- Granulation Technology
  - Purpose and batch technologies
- Continuous Granulation
  - From blending to tableting
  - Modular Approach
  - Benefits
- Core Technology
  - Twin Screw Granulator
  - Continuous Fluid Bed Dryer
- Experimental Data
- Achema 2012

Purpose of Granulation

- Granulation is a size enlargement process of particles
- 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
  - etc.

Granulation

Wet granulation involves the agglomeration of a mix of dry primary powder particles using a granulating fluid.

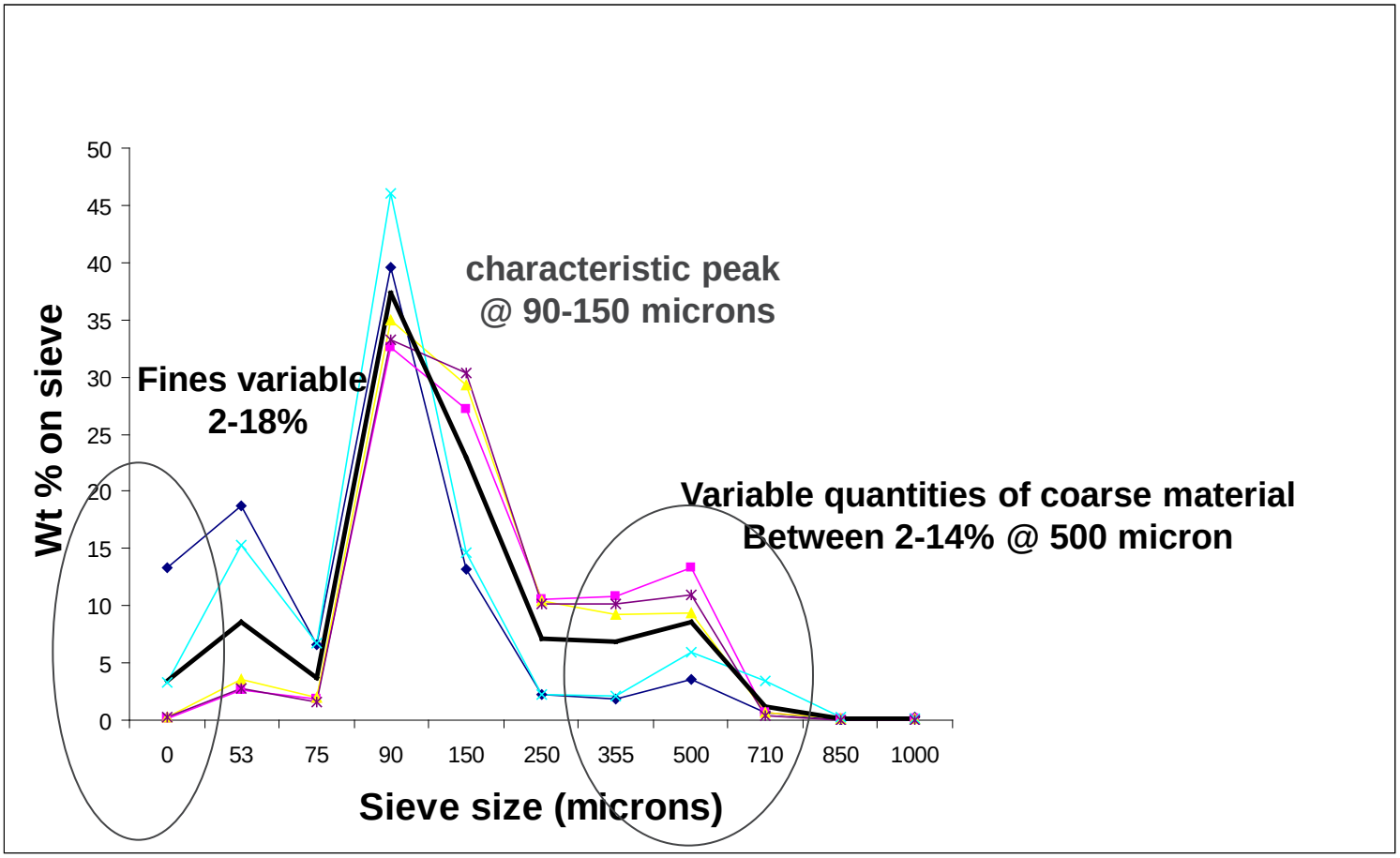
The fluid, which is added during the granulation step, must be pharmaceutically safe and volatile enough so that it can be evaporated by a subsequent drying step.

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.

Batch Granulation Technology

- Traditional batch processes
  - High shear mixers
  - 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 (Active Pharmaceutical Ingredient) required
- Difficulty to produce small samples on production scale equipment.

Comparison of materials – example of batch mixed granules



Source ISPE Conference
John Robertson
GlaxoSmithkline

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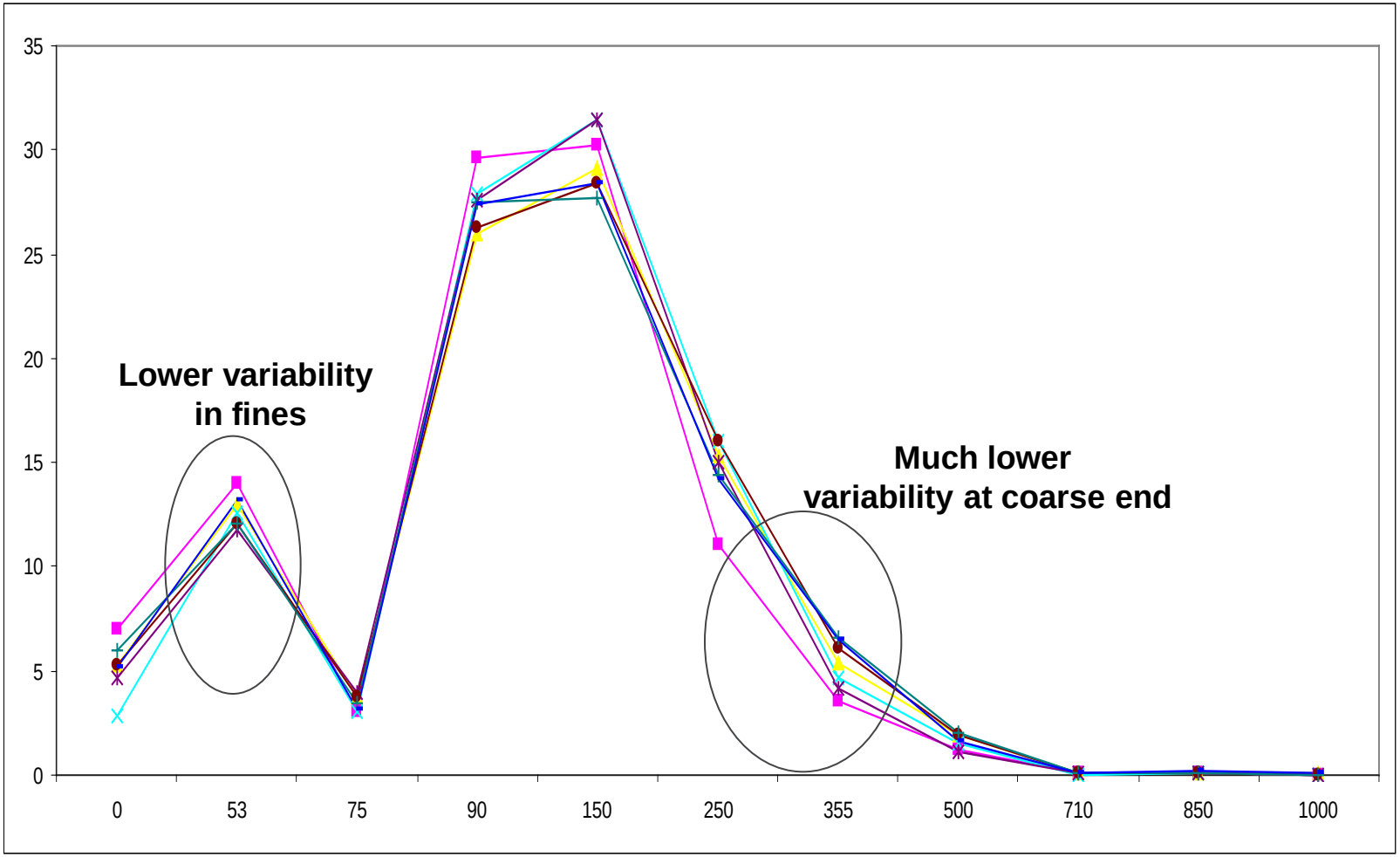
Comparison of materials – example of batch mixed granules



Potential for more consistent process !

Source ISPE Conference
John Robertson
GlaxoSmithkline

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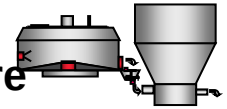
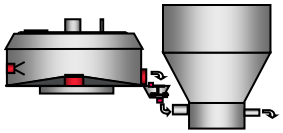
Batch vs. Continuous Granulation

3-10 litre

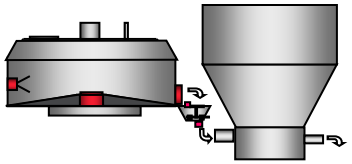
Phase 1

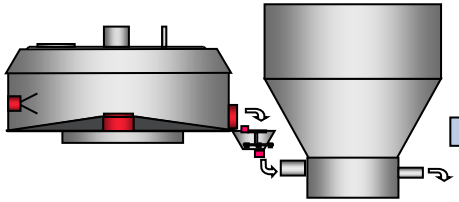
65-150 litre





Phase 2





Phase 3

300-600 litre

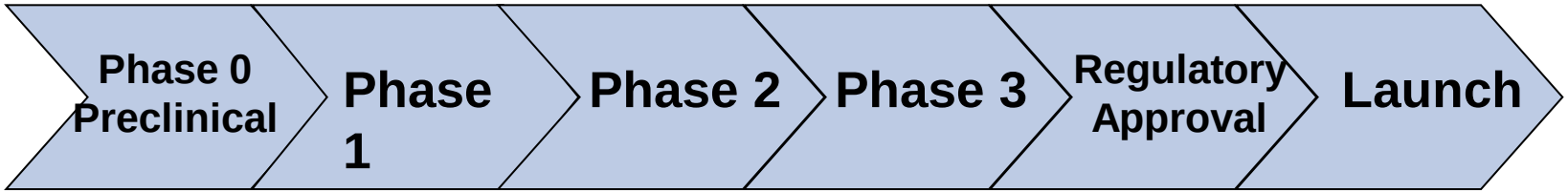
Pharmalab 16mm

Phase 1

Phase 2 and Phase 3

Pharmalab 24mm

Thermo Fisher Pharmaceutical Extruders

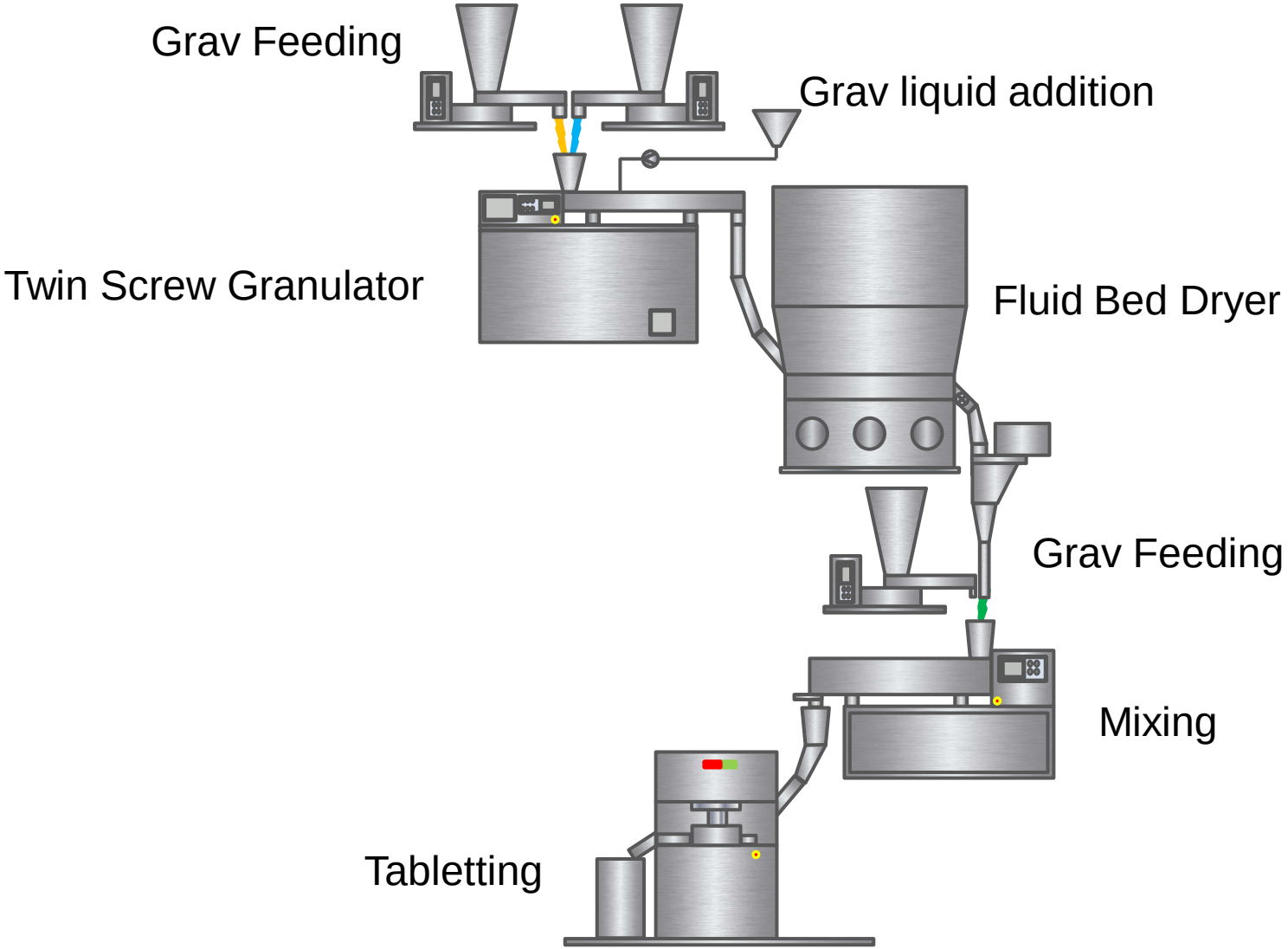


Chemistry	Medicinal	Kilogramme Lab	Process Chemistry Development	Production Development	Commercial Manufacturing
Available API	mg - g	1-10 kg	10 – 100 kg	1,000 kg	1,000 kg
Process Batch	20 g	1 – 5 kg	5 – 50 kg	100 – 500 kg	1,000 kg
Twin screw Extruder	**Pharma 11**	**Pharma 16**	**Pharma 16** **Pharma 24**	**Pharma 24**	**Pharma 24** ***Pharma 36***
Process Output	**20 g**	**1 – 5 kg/h**	**1 – 5 kg/h** **5 – 25 kg/h**	**5 – 25 kg/h**	**5 – 25 kg/h** ***25-100 kg/h***

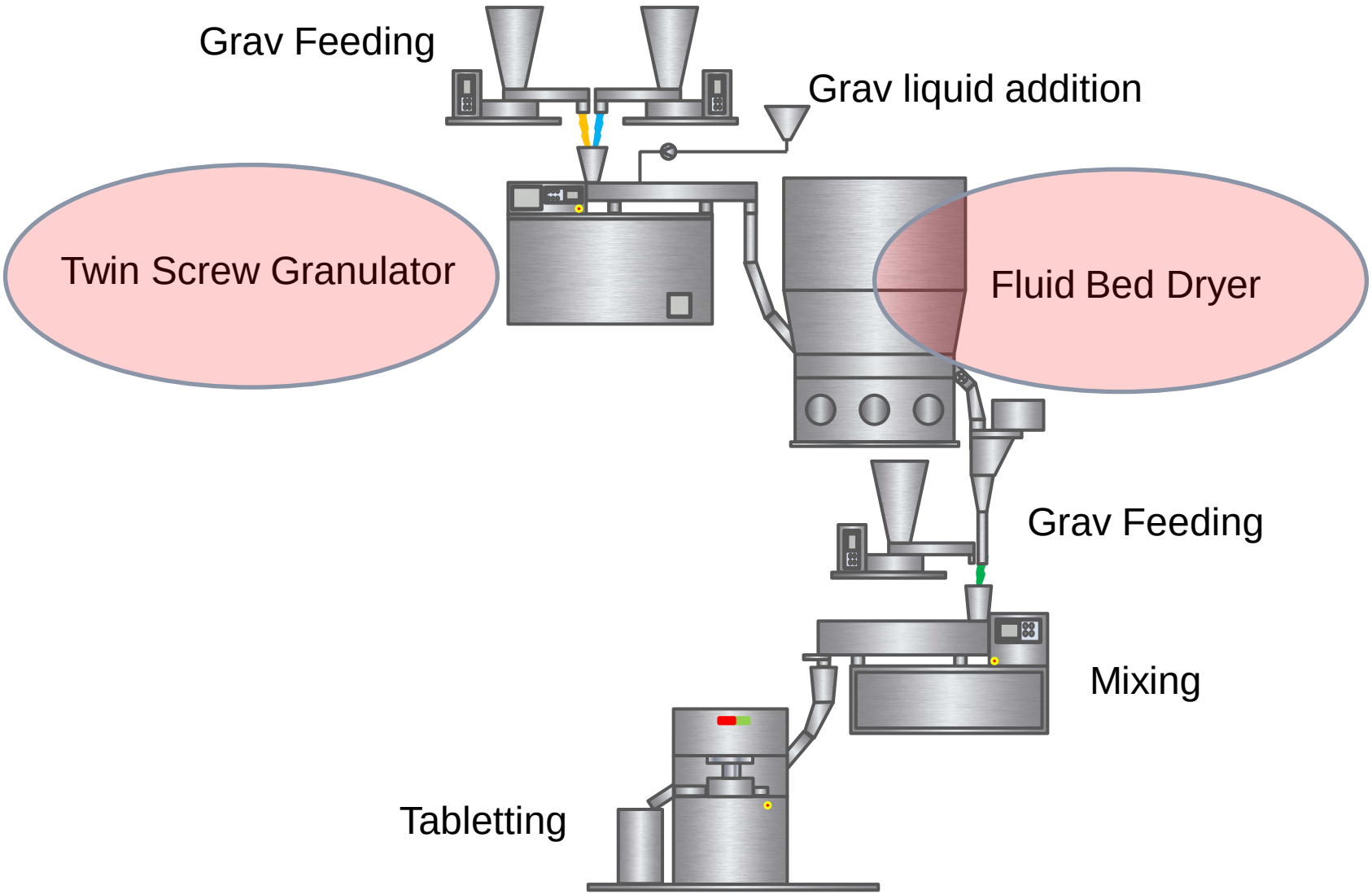
Benefits and Advantages of a Continuous Process

- Easier to enclose the whole process
  - *Smaller scale equipment*
  - *Small Footprint*
- Flexibility of batch size
  - *Small amount of materials in process*
  - *Improved control and consistancy*
- Elimination of dispensing
  - *Reducing risk of operator error in weighing out ingredients.*
  - *Reduced handling of / exposition to all ingredients*
  - *Reduce labour cost*
- *Possibility of implementing PAT*
  - *Automation*
  - *Process understanding*

How can a continuous, modular approach look like



Core processes for cont granulation



Pharma 16 Twin Screw Granulator

Gravimetric Screw Feeder

Liquid Feeding Pump

Pharma16 TSG Twin Screw Granulator

Pharma 16 TSG with powder bridge braker

Pharma 16 TSG showing discharge area

PharmaLab 16 Barrel Close-Up

Barrel Clamps Removed

Barrel Top Half and Screws Removed

Lower Barrel Front Section Removed

All Lower Barrel Sections Removed

Pharma 16 HME - maximum flexibility…

flexible screw configuration

Pharma 16 HME - Screw Elements:

Conveying elements:

Profiles with long helix are used:

- in the feeding sections
- - for degassing (venting)

Profiles with short helix are used:

- for high pressure built up
- in front of kneading elements

Pharma 16 HME - Screw Elements:

Mixing Elements :

- **Mixing Elements are used to introduce shear energy to the extruded materials.**
- **The disks are arranged in different offset angles used for:**

  - shearing
  - mixing
  - dispersing

Pharma 16 HME - Screw Elements:

Distributive Flow Elements :

- **Distributive Flow Elements are special mixing elements, used for the distribution of small quantities of additives and shear sensitive materials.**
- **Used to break up agglomerated granules.**

Pharma 24 Twin Screw Granulator

Gravimetric Screw Feeder

Gravimetric Liquid Feeding Pump

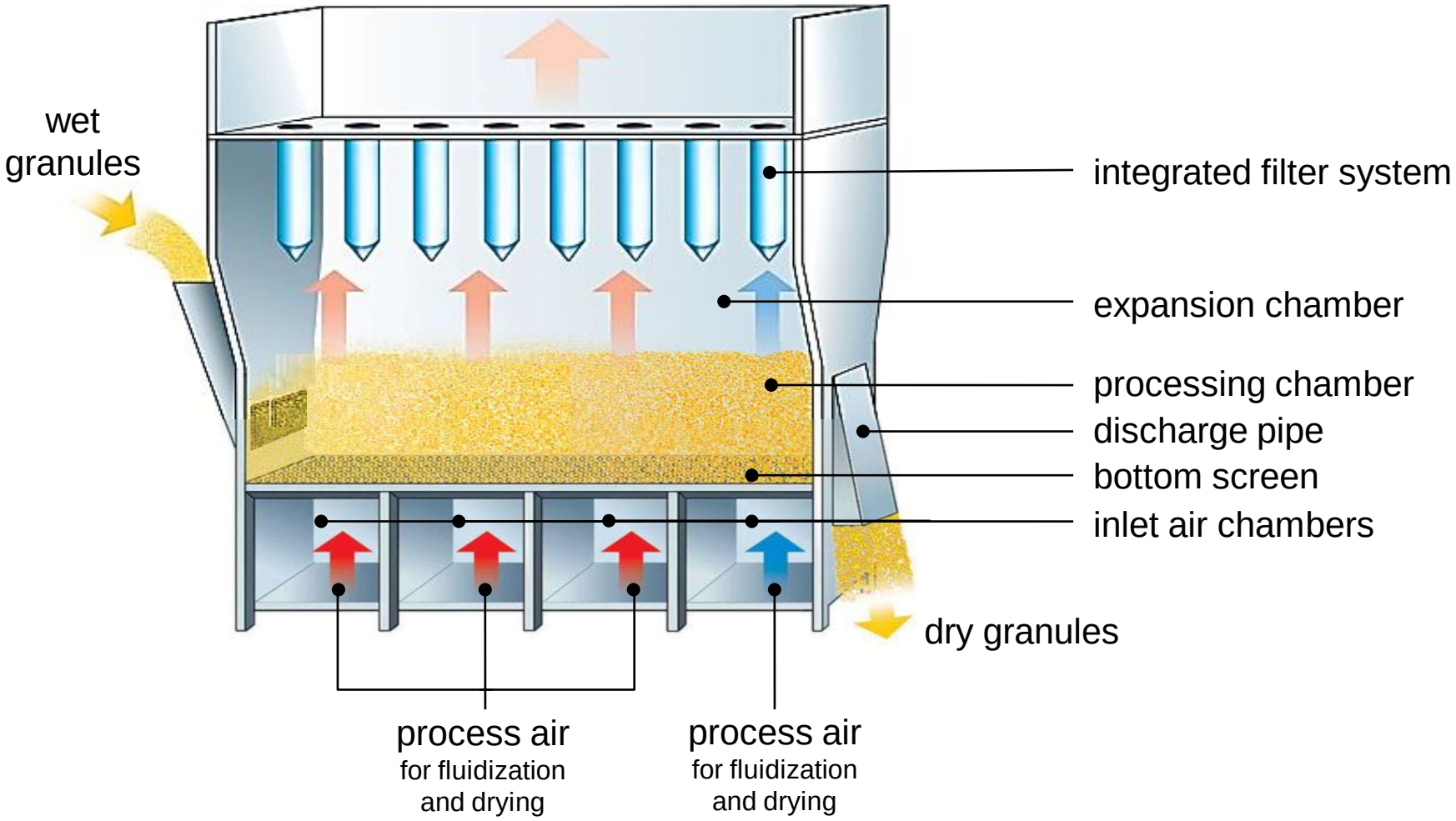
Crammer Feeder

Pharma 24 TSG Twin Screw Granulator

Pharma 24 TSG with feeder platforms

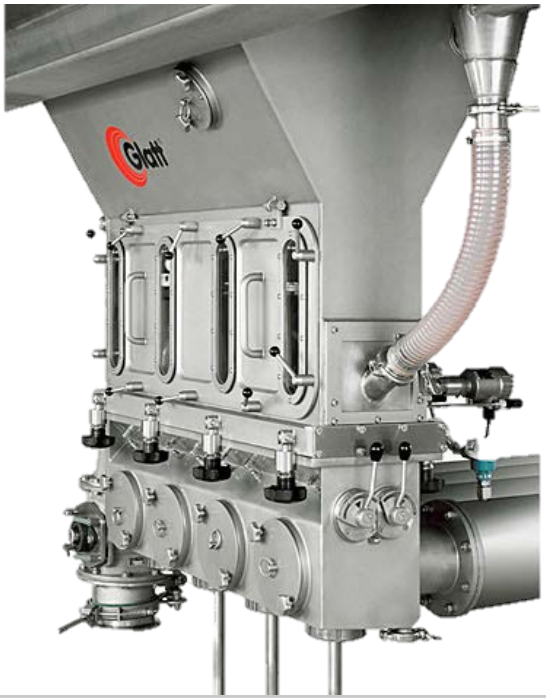
Continuous Fluid Bed Drying

- Principle theory of continuous fluid bed drying



Continuous Fluid Bed Drying

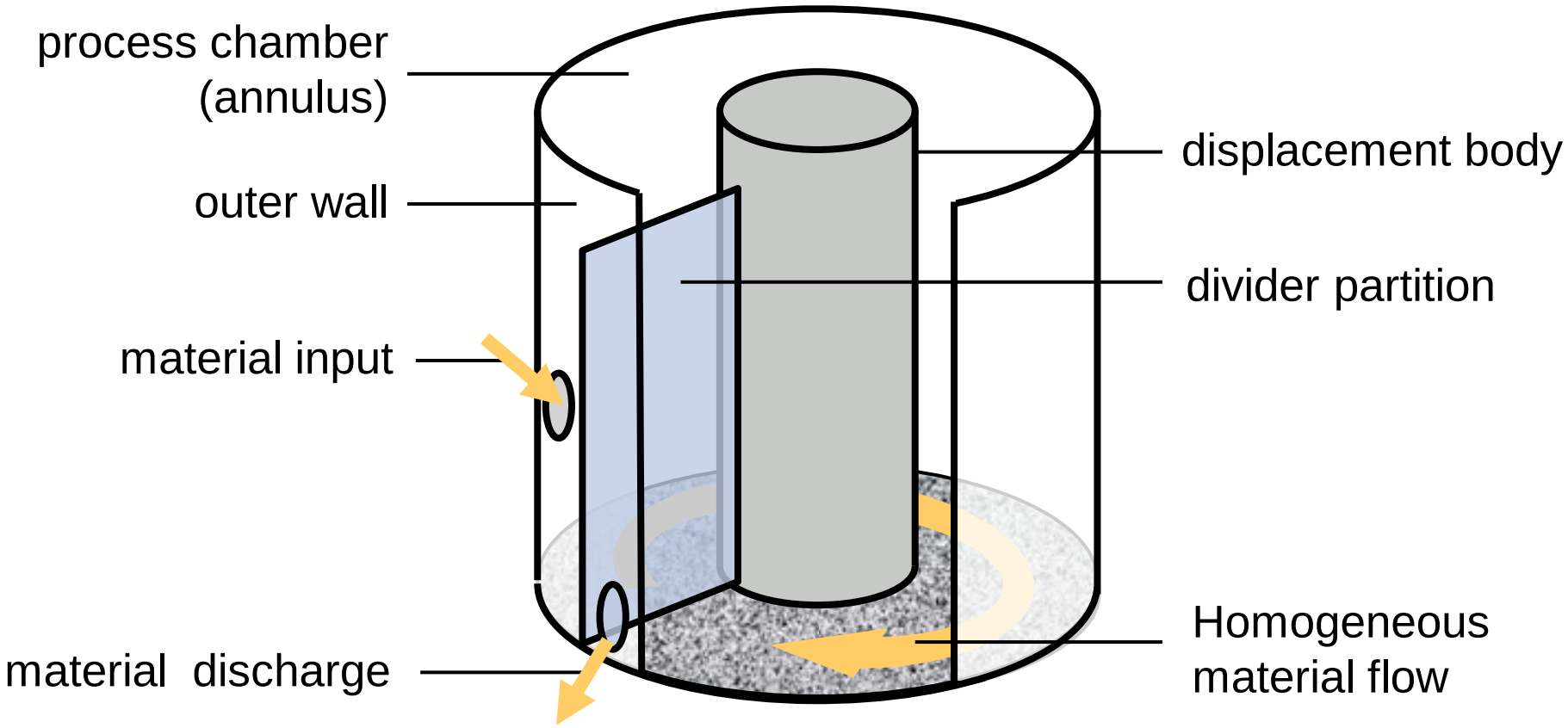
- Equipment size



throughput	< 15 kg/h	> 10 kg/h
shape	round	rectangular
name	GF 5	GF 25, 50 & 125
implementation	Insert for GPCG 2 LabSystem	stand-alone machine

Continuous Fluid Bed Drying

- Principle GF5: ring-shaped process chamber



Continuous Fluid Bed Drying

- Process development with GPCG 2 LabSystem

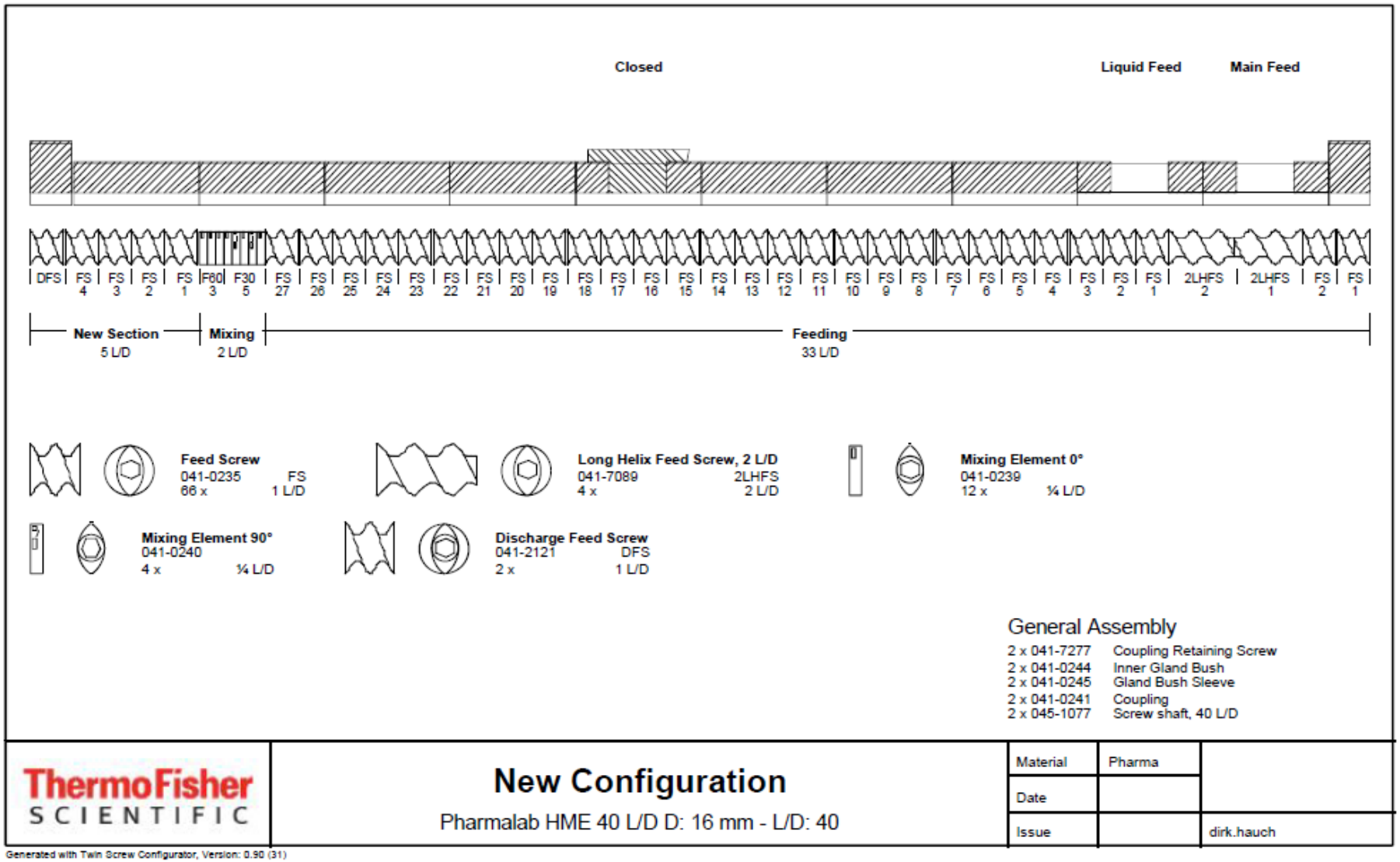
Process overview

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

Continuous Fluid Bed Drying

- GPCG 2 LabSystem with GF5

Experimental Data



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Experimental Data

Formulation :

	Qty (kg)	Proportions (%)*
API	8.0369	80.369
Aerosil	0.0557	0.557
Sodium starch glycolate	1.003	10.030
Cellulose MRK (microcr. Cellulose)	0.5701	5.701
Hypromellose Pharmacoat 603 (HPMC)	2.3400	3.343

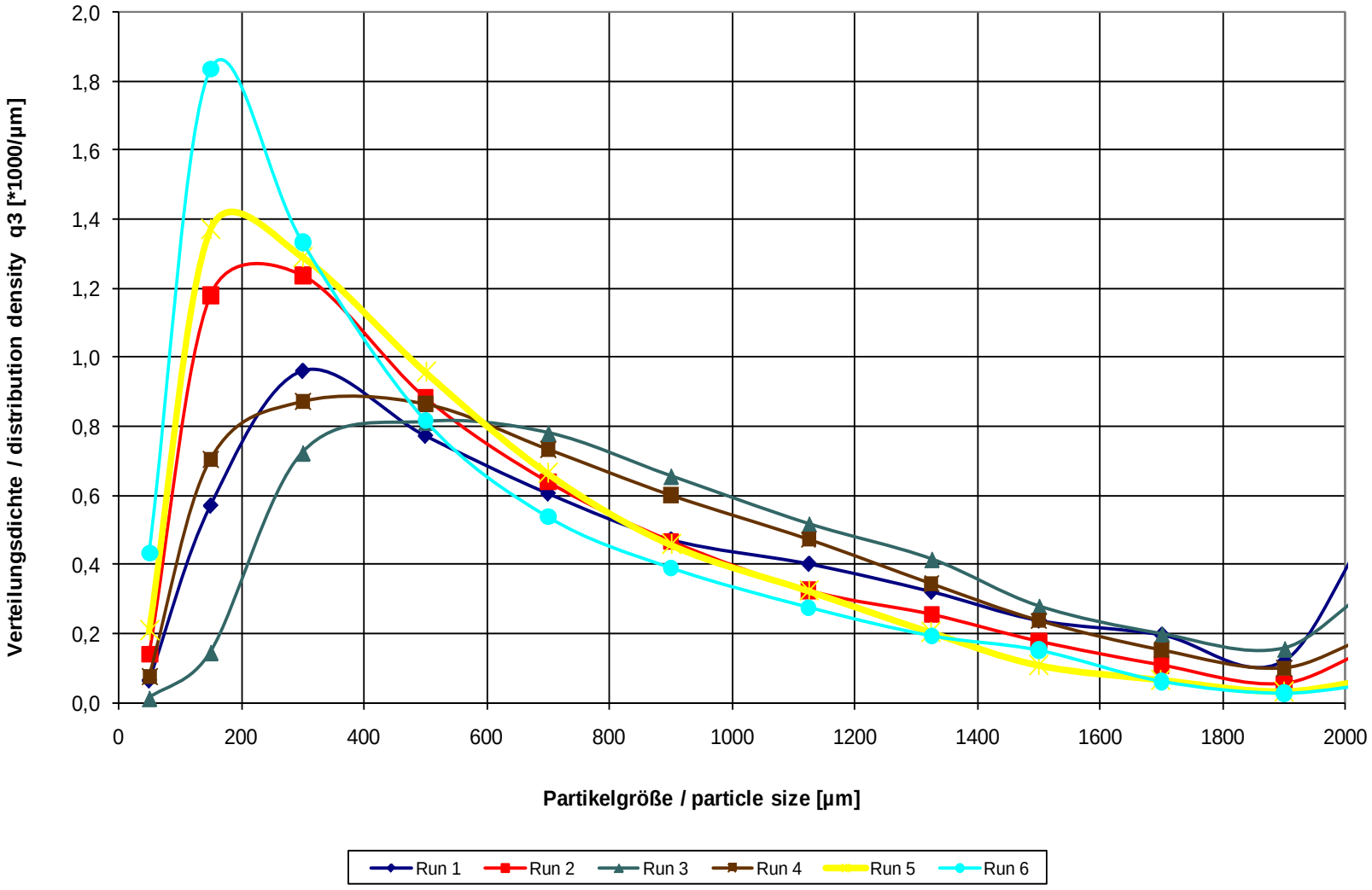
Barrel Temperature 35°C
Pure water as liquid addition

Experimental Data

Parameters	X1 Screw speed [rpm]	X2 Spray rate [g/min]	X3 Kneading element config. [°]
-1 low	300	28	7x30, 1x60
0 center	450	31	5x30, 3x60
+1 high	600	35	3x30, 5x60

6 consecutive experiments DoE with Parameters X1, X2 and X3

Experimental Data



Achema 2012 Set-Up

- Achema
- 18th – 22nd July, Frankfurt (Germany)
- Hall 3.0 Booth F1

- Pharma 16 TSG
- GPCG2 with GF-5

Thank you for your attention !

Any questions ?

Looking forward to see you at Achema !