ThermoFisher SCIENTIFIC

Pharma Twin Screw Extruders 2010

The world leader in serving science

The World Leader in Serving Science

We are the leading provider of analytical instruments, equipment, reagents and consumables, software and services for research, analysis, discovery and diagnostics.

Leading Brands

Thermo SCIENTIFIC

Fisher Scientific

Size and Scale

- $10.5 billion in revenues
- 35,000 employees in 40 countries
- Serving 350,000 customers in 150 countries
- Fortune 300 company

Unmatched Capabilities

- Complete portfolio
- World-class technologies
- Commercial and service strength

The World Leader in Serving Science

Thermo SCIENTIFIC

Fisher Scientific

Thermo's world-class analytical technologies

+

New capabilities acquired from Fisher

- New brand stands for innovation and quality
- Thermo instruments plus *new* reagents, consumables and equipment
- Even better laboratory workflow solutions

Famous catalogs and supply-chain services

- Mark of choice and convenience
- Complete product portfolio of equipment & supplies
- One-stop, total lab supplier

All from Thermo Fisher Scientific

ThermoFisher SCIENTIFIC

The Thermo Scientific brand

Historical brand names part of ThermoScientific:

ThermoFisher SCIENTIFIC

Pharma Twin Screw Extruders 2010

Hot Melt Extrusion

Twin Screw Granulation

Information HME

Product Portfolio HME

Information TSG

Product Portfolio TSG

Customized Solutions

Introduction HME

HME – What‘s your challenge today?

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Where is pharmaceutical Hot Melt Extrusion?

"For both the pharmaceutical industry and the academic community HME became an innovative drug delivery technology that is receiving increased attention. HME turned now into highly dynamic, interdisciplinary topics that provide a creative link between engineering and pharmaceutical sciences for the purposes of drug delivery.

Research in these vibrant research areas is making significant advances resulting in innovative, engineered drug delivery systems."

Source:
G. P. Andrews, Phil. Trans. R. Soc. A (2007) 365, 2935–2949

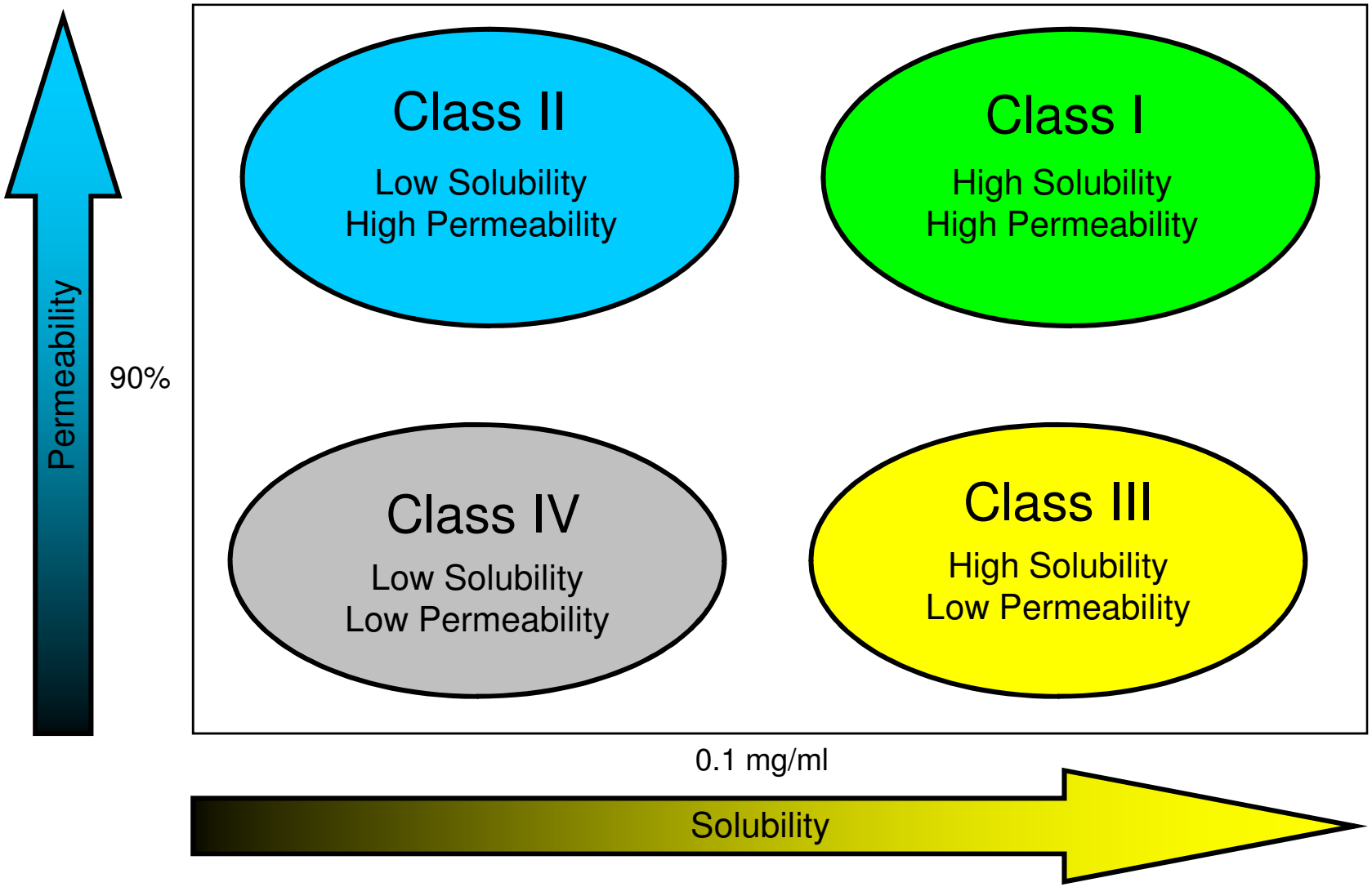
What is Hot Melt Extrusion?

Processing of polymeric materials above their glass transition temperature (T_g) in order to effect molecular level mixing of thermoplastic binders and/or polymers and active compounds

Melt extrusion is a combination of melting and mechanical energy with advantages like:

- Continuous
- Reproducible
- Reasonably high throughput
- Dust reduction
- On-line-monitoring

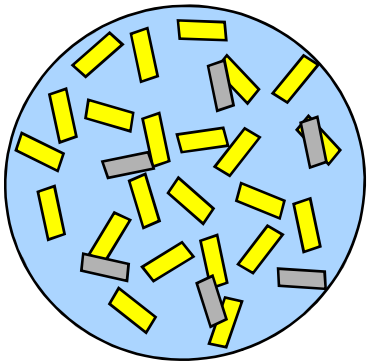
Biopharmaceutics Classification Scheme

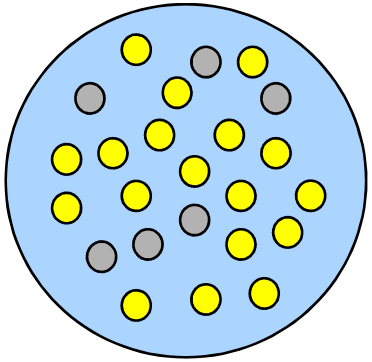


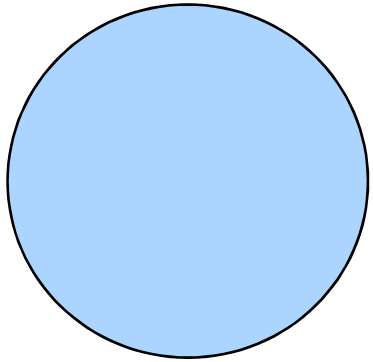
Why Hot Melt Extrusion

	Problem	Solution
1	Poor API stability during processing	Use of melt extrusion as alternative to wet agglomeration (no hydrolytic stress, no drying)
2	Poor (low/unreliable) bioavailability due to poor API solubility	Use of melt extrusion to prepare solid dispersion or SEDDS (=enhanced dissolution)
3	Poor compliance due to short dosing interval (=short half life of API)	Use of melt extrusion to prepare sustained release dosage form (single/multiple units)
4	Poor stability or tolerability of API in stomach	Use of melt extrusion to prepare enteric dosage form (single/multiple units)
5	Poor taste of API	Use of melt extrusion to prepare taste-masked pellets
6	Special dosage form designs (films, rods, hollow cylinders etc.)	Use of melt extrusion to achieve special shape

Different Types of Solid Dispersions/Solutions







Polymer:	amorphous	amorphous	amorphous
Drug:	crystalline	amorphous	molecularly dissolved
Thermo-dynamic Stability	almost stable	unstable (kinetically controlled)	stable (drug below saturation solubility)

Pharmaceutical Development Needs

- **Consistent, small scale production.**
- **Low consumption of expensive materials**
- **Easy cleaning with simple verification.**
- **Flexibility for new product development.**
- **Reliable and repeatable operating conditions.**
- **Accurate process data for product audit.**

How Extrusion Technology can support you…

- Hot melt extrusion supports you by establishing stable solid solutions which increase the availability of poorly soluble ingredients,
- A continuous steady state process monitored by process control allows you to minimize failed batches
- Extrusion technology allows you to produce new drug dosage forms e.g. mini implants
- Melt extrusion allows you to reduce the consumption of solvents - for instance in comparison with the wet granulation process
- and many other good reasons …

Extrusion technology is a mature process used in the polymer industry for more than 40 years and in the pharmaceutical for approx. >20 years known.

Validation Aspects

Regulatory aspects of melt extrusion:

Hot melt extrusion has a comprehensive documentation, which satisfy regulatory authorities

Melt extrusion is a mature technology

Measurable parameters such as feeding rate, equipment temperatures, discharge pressure, vacuum control, etc. can be monitored on-line with local sensors. Data logging provides supporting documentation to ensure the quality of production lots and simplify quality control.

Use of in-line sensors PAT provide a good basis for the FDA – QbD initiative

Product Portfolio HME

Twin Screw Solutions for HME

24 mm Line

PharmaLab 24

16 mm Line

EuroLab

PharmaLab 16

MiniLab

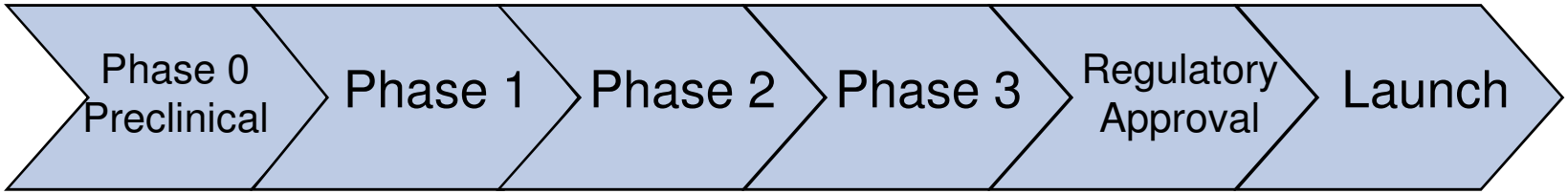
MiniLab

Pharma MiniLab

Phases of Pharmaceutical Development

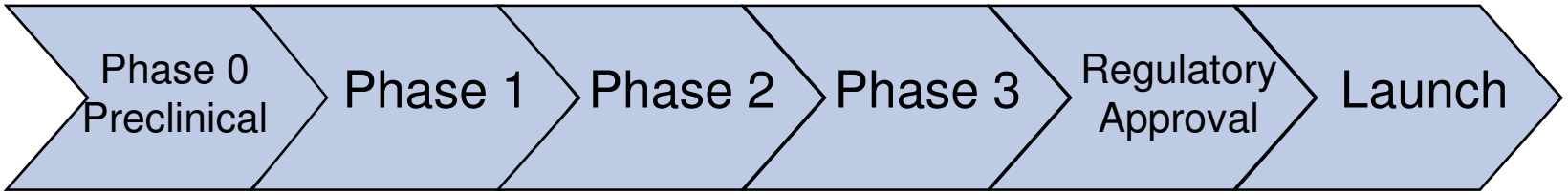
Constraints

- Quantity of API
- Quality of API
- Consistent quality of Drug product
- **Time**



Chemistry	Medicinal	Kilogramme Lab	Process Chemistry	Production Site	Production Site
API Batch Size	mg - g	0.2 -10 kg	10 – 100 kg	1,000 kg	1,000 kg
Process Batch	10 g	0.2 - 5 kg	5 – 50 kg	100 – 500 kg	500 kg
Testing	In Vitro & Animal	Safety in Human	Safety and Efficacy	Market	Market

The Solution for your Phase



Chemistry	Medicinal	Kilogramme Lab	Process Chemistry	Production Site	Production Site
API Batch Size	mg - g	0.2-10 kg	10 – 100 kg	1,000 kg	1,000 kg
Process Batch	10 g	0.2-5 kg	5 – 50 kg	100 – 500 kg	500 kg
Twin Screw Granulator	**Pharma Minilab**	**PharmaLab 16**	**PharmaLab 16** **PharmaLab 24**	**PharmaLab 24**	**PharmaLab 24** *scale out*
Process Output	10 g	0.2-5 kg/h	0.2 – 5 kg/h 1 – 50 kg/h	1 – 50 kg/h	1 – 50 kg/h *25 – 100 kg/h*

The MiniLab

HAAKE MiniLab – suitable e.g. for

- **Proof of concept studies**
- **Creating specimen for drug delivery systems**
- **Your advantages of a Micro Compounders**
- Substantial cost savings for proof of concept studies due to compounding of small quantities of ingredients (5 ml)
- Understanding of material characteristics by documenting structural changes via integrated viscosity measurement
- Flexible process conditions for different materials by
  - Using conical or co- rotating screws
  - Automatic bypass operation for extrusion/recirculation
  - Force feeder especially for continuous powder feeding

Pharma MiniLab for Small Scale Production

HAAKE Pharma MiniLab

- Allows you e.g. to produce clinical trial samples for e.g. phase 1 when only a few grams of clinical material is needed
- No time delay due to long process development on a larger twin screw extruder
- The characteristics of our GMP Version are
  - Without backflow channel
  - Force feeder for powder and small pellets
  - Stainless steel materials without painted parts
  - Password protected Software

Pharma MiniLab Features

Housing

- No Painted parts
- All sheet metal is made of stainless steel 1.4301 (304)
- Air supply connectors made of stainless steel
- Force feeder for powder

New developments of our standard Pharma MiniLab:

We are currently working on our next generation model which will show improvements regarding cleaning features with an open outlet area.

MiniLab Force Feeder for continuous feeding

Force Feeder

- Stainless steel No. 1.4404 (316 L)
- Roughness electro polished better than 0,8µm

Force Feeder Screw

§ Stainless steel No. 1.4112 (440 B) – Passivated

§ Surface roughness 0,8 µm.

EuroLab Pharma

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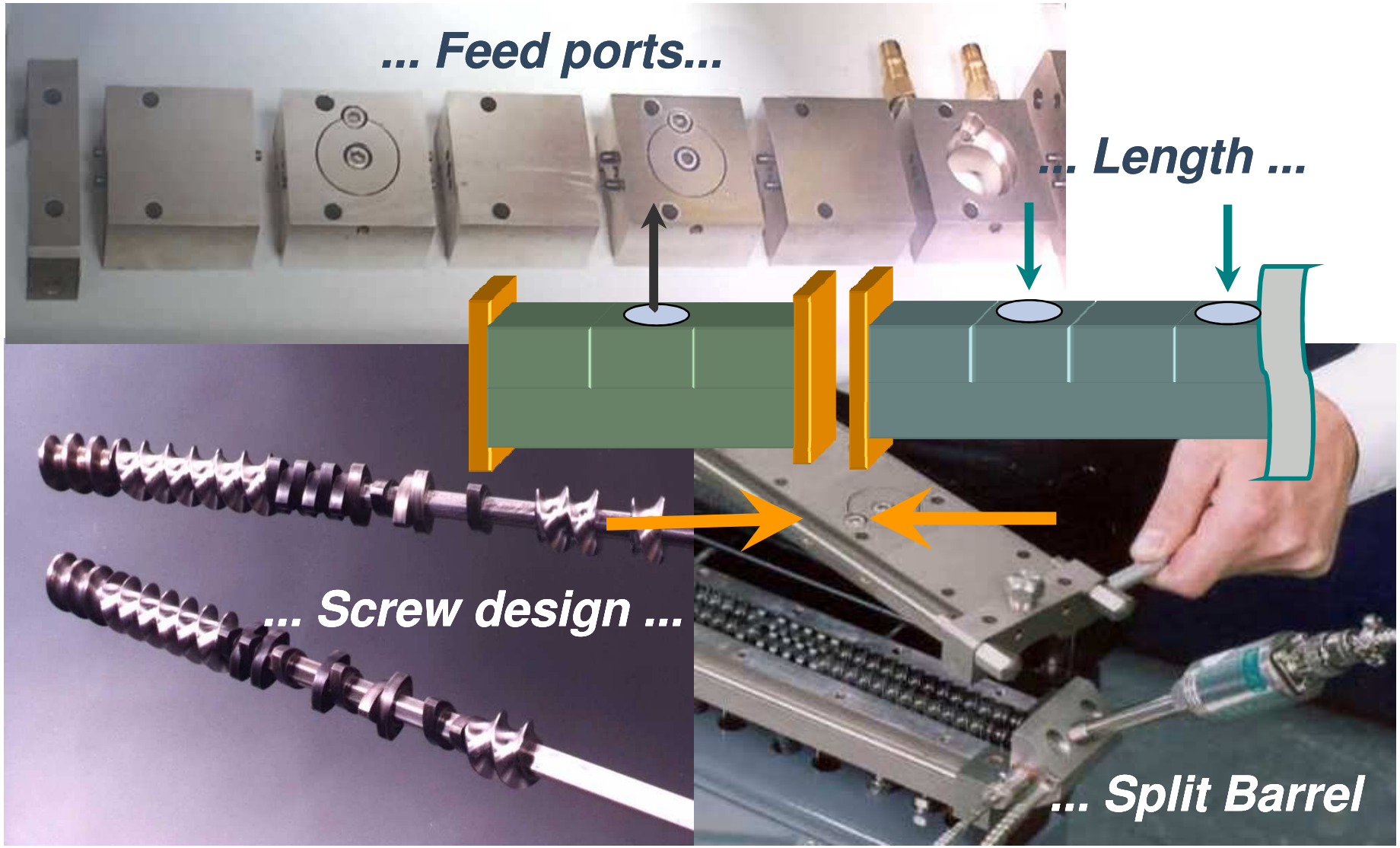
EuroLab Pharma - maximum flexibility…



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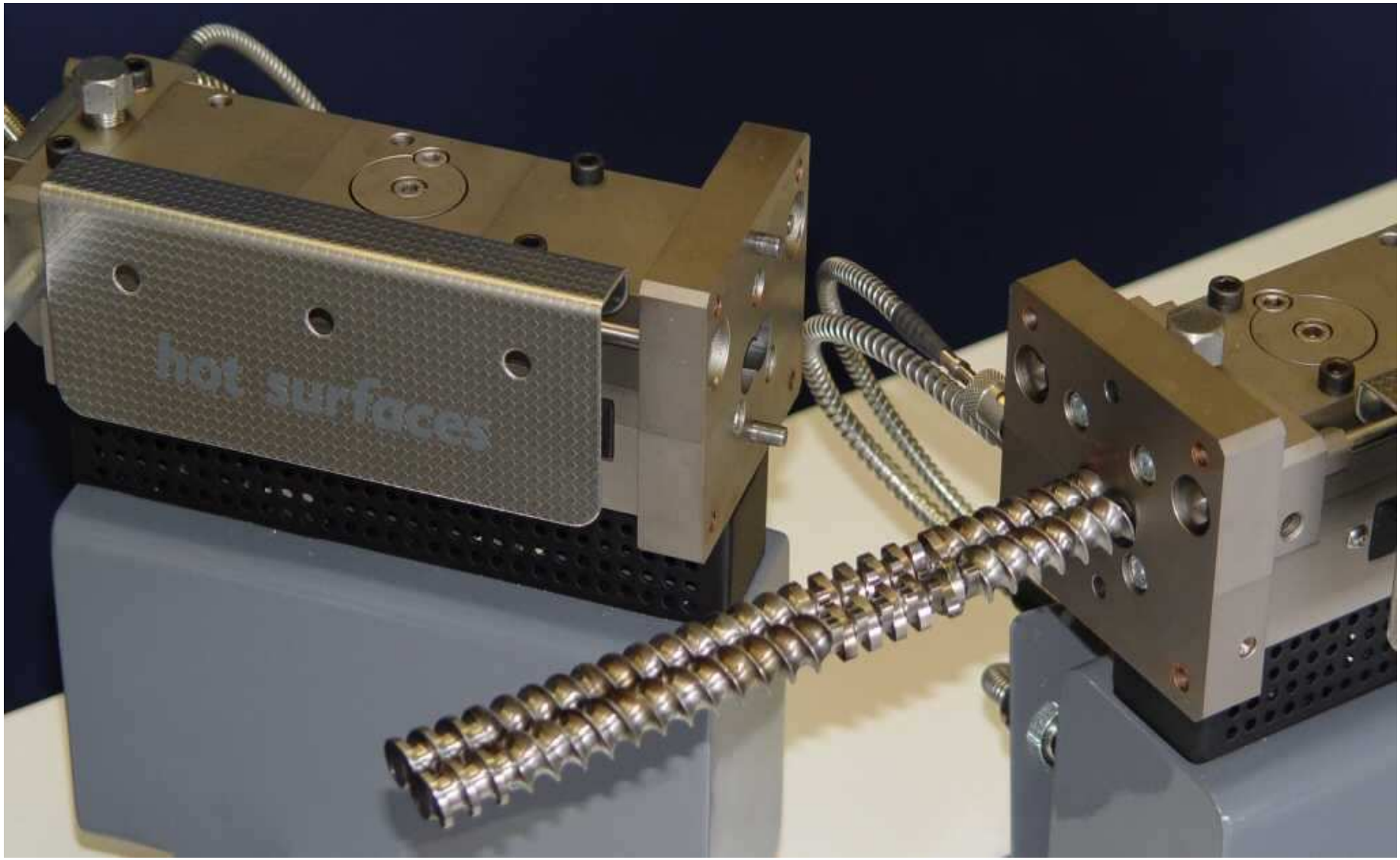
EuroLab Pharma - maximum flexibility…

flexible screw configuration

EuroLab Pharma - maximum flexibility…

EuroLab Pharma - maximum flexibility…



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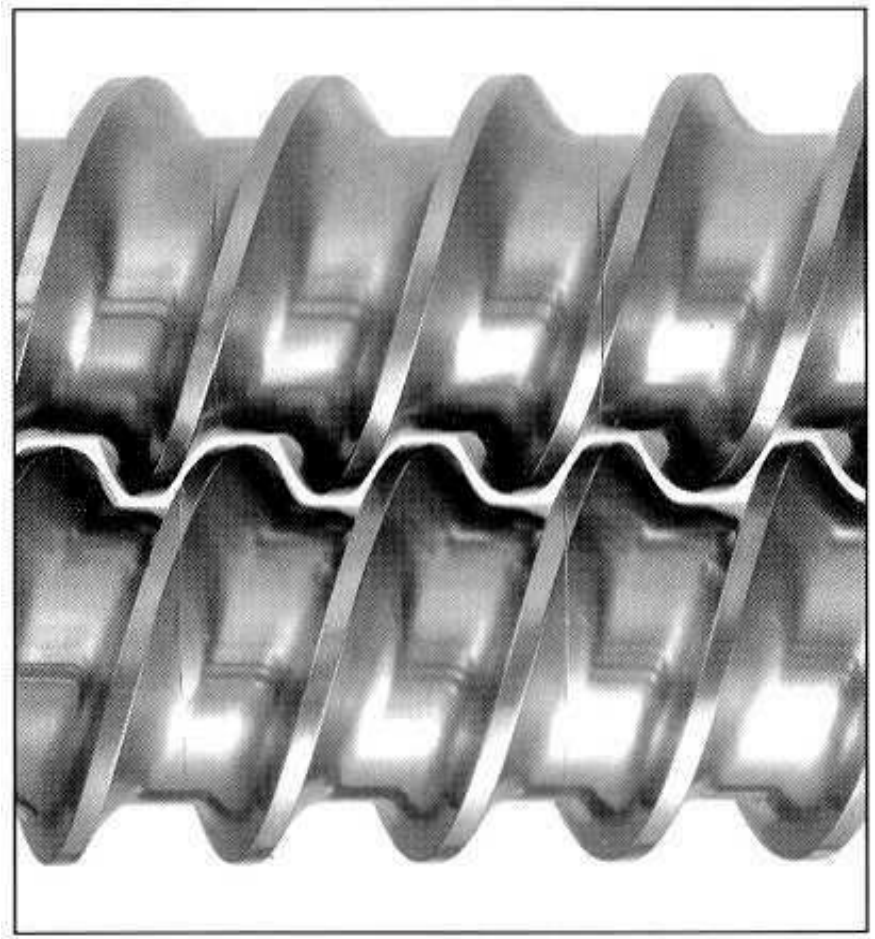
Parallel twin-screw extruder - Screw Elements:

Conveying elements:



Profiles with open chambers are used:

- in the feeding sections
- for melt exchange (longitudinal mixing)
- for degassing (venting)

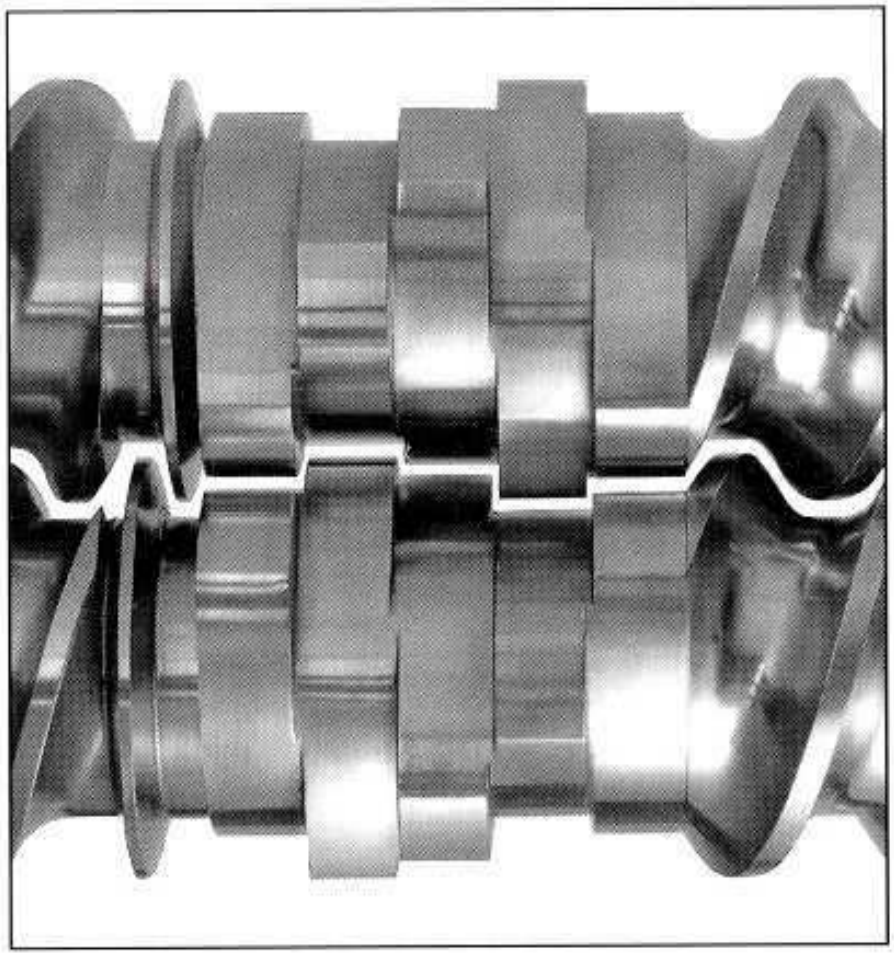
Profiles with closed chambers are used:

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

Rheomex PTW – Conveying Elements

Parallel twin-screw extruder - Screw Elements:

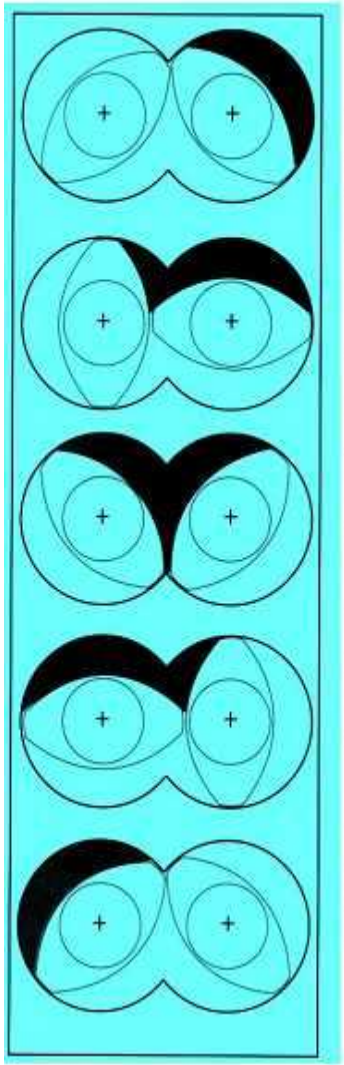
Mixing Elements :



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

  - plasticizing
  - shearing
  - mixing
  - dispersing

Mixing elements



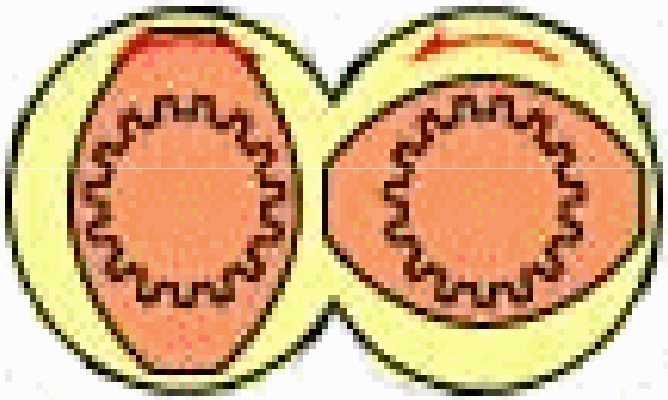
TWIN-SCREW MIXING

Material follows a figure '8' path as it is constantly transferred from one screw to the other across the intermesh.

The mixing action is a combination of compression and expansion with smearing effects between screw to screw and screw to barrel wall

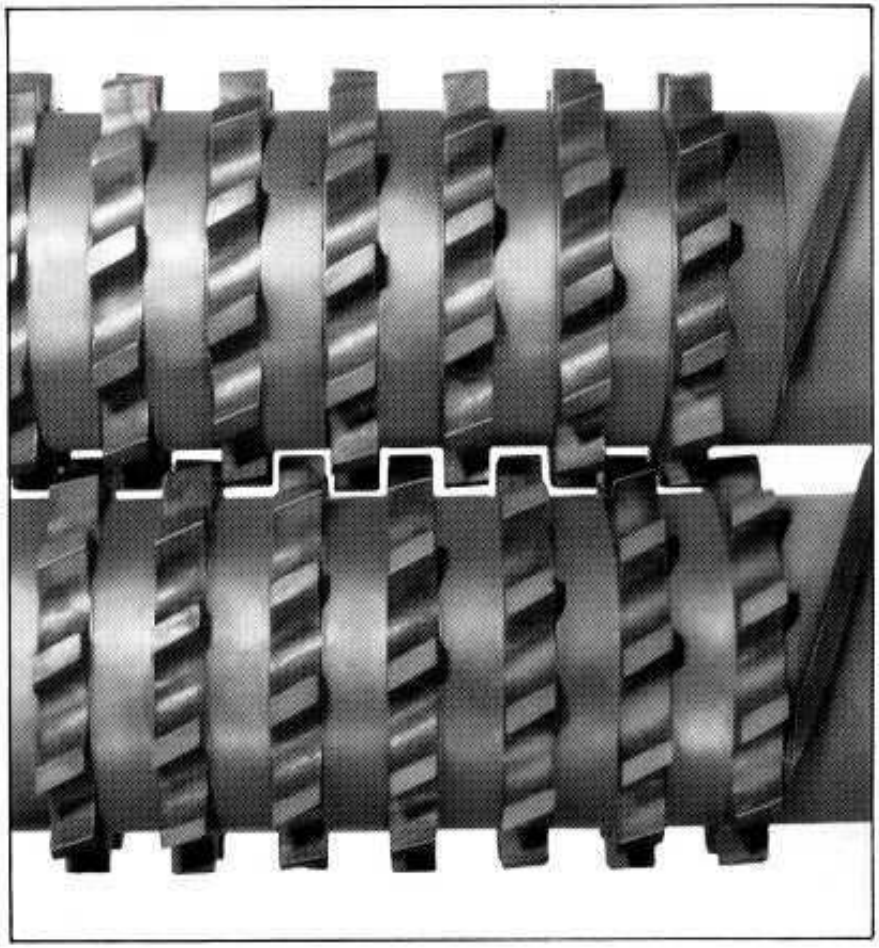
The energy to melt the polymer comes from the mechanical energy of the shafts, (i.e. from the motor)

Inter-particulate friction causes rapid melting, and high shear is imparted during the high viscosity transition from solid to molten phase.



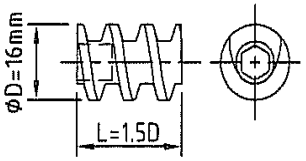
Parallel twin-screw extruder - Screw Elements:

Distributive Flow Elements :

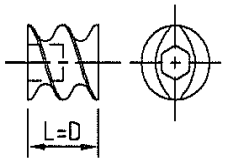


- **Distributive Flow Elements are special mixing elements, used for the distribution of small quantities of additives and shear sensitive materials.**
- **The shearing energy introduced to the polymer is significantly lower than that of the kneading elements.**

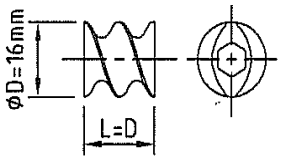
Screw elements:



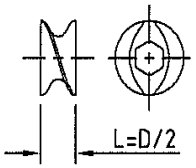
SINGLE LEAD
EXTRUSION SCREW
0° 040-0126 - Front
90° 040-0127 - Rear



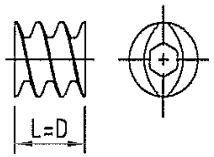
TWIN LEAD
DISCHARGE SCREW
040-0521 - Normal
040-4284 - Reverse



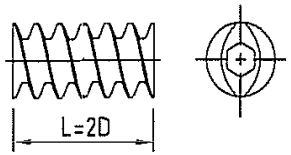
FEEDSCREW
040-0107 - Normal
040-1568 - Reverse



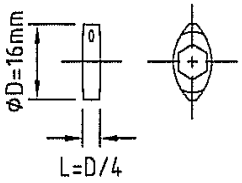
HALF FEEDSCREW
040-0274 - Normal
040-2745 - Reverse



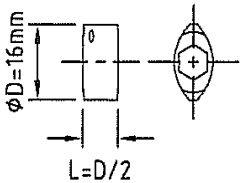
FEEDSCREW
041-6023 - Short helix
041-6024 - Long helix



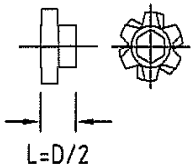
2D FEEDSCREW
041-4175 - Normal helix
041-5898 - Short helix
041-5899 - Long helix



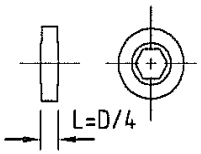
MIXING ELEMENT
040-0104 - 0° offset
040-0105 - 90° offset



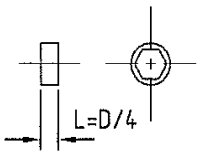
D/2 MIXING ELEMENT
041-2631 - 0° Offset
041-2632 - 90° Offset



DISTRIBUTIVE FLOW
ELEMENT
041-9999 - Quarter depth
042-0000 - Half depth

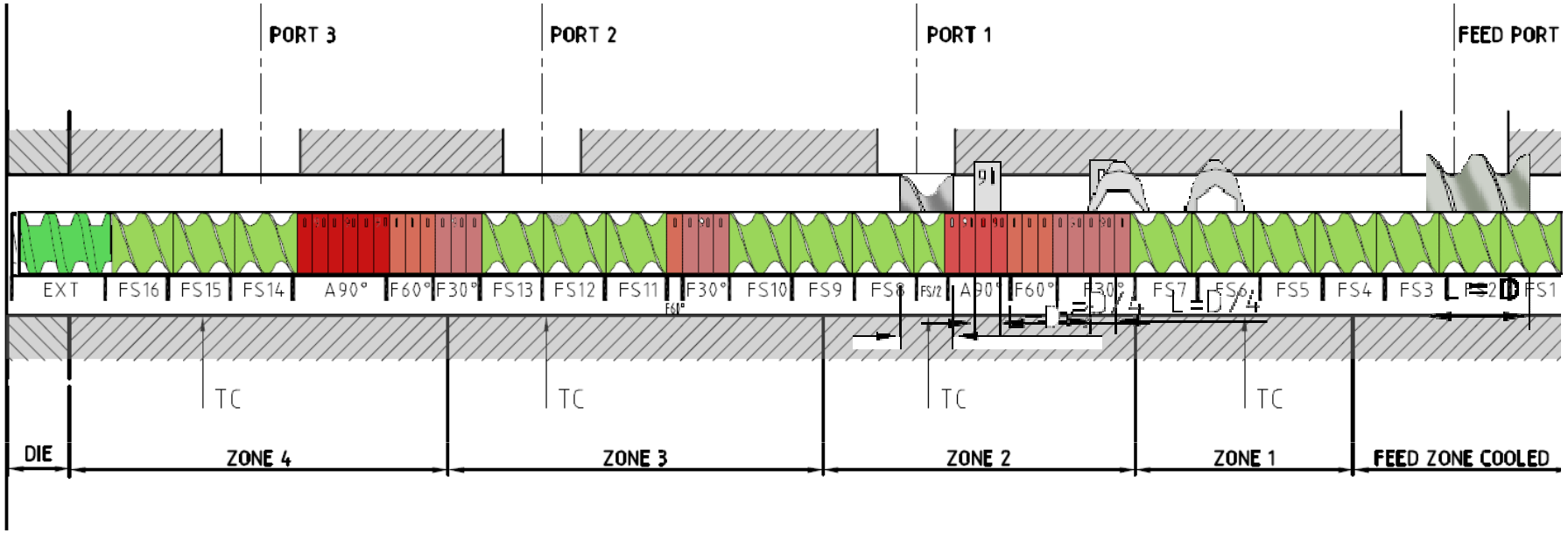


FLOW RESTRICTOR
ELEMENT
045-0135 - Ø 15.1 mm
045-0133 - Ø 15.6 mm
045-0134 - Ø 14.6 mm



FLOW RESTRICTOR
SPACER
040-0272

Screw configuration (Standard Layout 75%)



Feed Screw

- Conveying sample
- only partly filled
- low shear

Mixing Element

- Melting & mixing
- completely filled
- high shear

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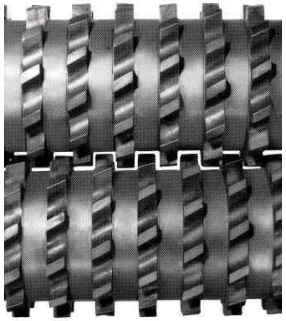
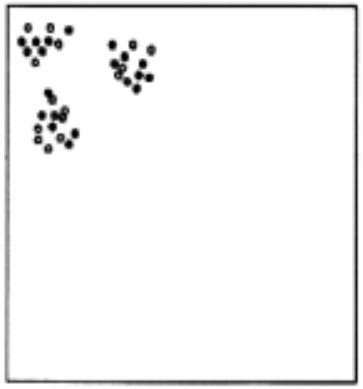
Dispersive and Distributive mixing

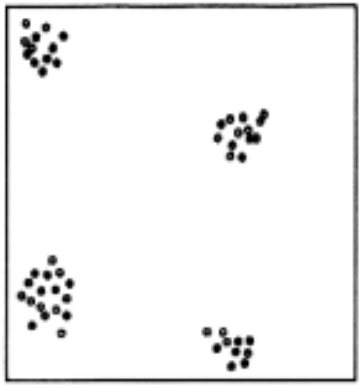
- For nearly all mixing applications a well dispersed and well distributed mixture is required.
- Distributive mixing can be achieved by splitting and reorienting the flow repeatedly
- Dispersive mixing can be achieved by passing the mixture through small regions of intense deformation.





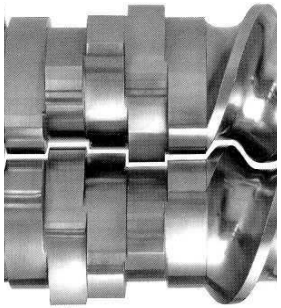
Poorly distributed

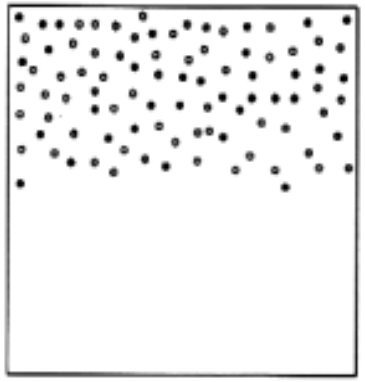
Poorly dispersed



Well distributed

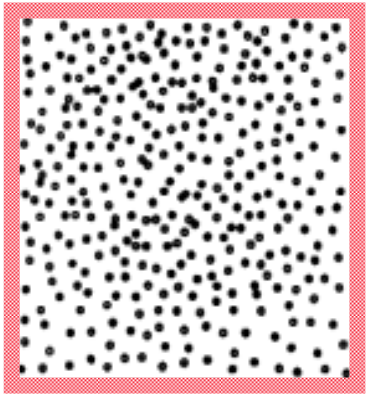
Poorly dispersed





Poorly distributed

Well dispersed



Well distributed

Well dispersed

Mixing and composites, M. Kontopoulous Chee 18.2. p. 390presentation Queens Univer

EuroLab Pharma Features

- Product contact parts made from pharmagrade steel
- Material cerificates available
- Removable and segmented top barrel
- Touchscreen control
- Integrated feeding solutions
- Integration of PAT (e.g. NIR) possible

PharmaLab 16 and 24 – Technical Specs

		Pharma 16 HME				Pharma 24 HME			
Part Number	554-	1136	1146	1156	1166	2145	2155	2165	2175
Barrel Length	L/D	**25:1**	**25:1**	**40:1**	**40:1**	**30:1**	**30:1**	**40:1**	**40:1**
Barrel Bore Diameter	mm	16	16	16	16	24	24	24	24
Screw Diameter	mm	15.6	15.6	15.6	15.6	23.6	23.6	23.6	23.6
Channel Depth	mm	3.3	3.3	3.3	3.3	5.2	5.2	5.2	5.2
Centre-line Spacing	mm	12.5	12.5	12.5	12.5	18.75	18.75	18.75	18.75
Centre-line to Radius ratio		1.56	1.56	1.56	1.56	1.56	1.56	1.56	1.56
Maximum Screw speed	rpm	500	1000	500	1000	500	1000	500	1000
Power at Maximum Speed	kW	1.25	2.5	1.25	2.5	5.5	11	5.5	11
Torque per shaft	Nm	12	12	12	12	52.5	52.5	52.5	52.5
Torque/ (C-line^3)	Nm/cm^3	6.1	6.1	6.1	6.1	8	8	8	8
Barrel zones		6	6	10	10	6	6	8	8

PharmaLab 16 Hot Melt Extruder

PharmaLab 16 HME
Process development studies
Producing samples for Clinical Trials

Advantages of a Pharma HME
Substantial cost savings for process development from compounding of samples (from 200g)

Significant time savings from ability to process multiple samples in succession.

Flexible process configurations for different materials from segmented screws and barrels.

Opportunities for multiple feed streams to minimise use of expensive API.

Special feeding accessories for difficult to handle ingredients.

PharmaLab 16 Features

- Product contact parts made from pharmagrade steel
- Stainless steel housing
- Material cerificates available
- Full validation documentation available
- Removable and segmented top and bottom barrel
- Touchscreen control
- Integrated feeding solutions
- Automated start-up procedure available
- Integration of PAT (e.g. NIR) possible
- Based on casters, movable

PharmaLab 16 – Barrel and Screws Removal

Barrel clamps

Barrel clamps removed

Upper barrel removed

Lower liner and screws removed

PharmaLab 16 – Barrel and Screws Removal

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PharmaLab 16 – Design Features

Design features

Stainless steel GMP construction.
No external painted parts.
Sheet metal base is made of stainless steel.

Process contact parts from pharma-grade through-hardened surgical stainless steel

Easily removable screws and barrels for cleaning or reconfiguration.

Adjustment of effective process length to minimise residence time.

PharmaLab 16 – Segmented Barrel

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PharmaLab – Screw Length Adaption Kit

Adjustment of effective process length to minimize residence time.

Pharma 16 Air Cooled Conveyor Belt

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Pharma 16 – Varicut and Twin Servo Pelletiser

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Pharma 16 – Strand Pelletising Line

ThermoFisher SCIENTIFIC

PharmaLab 24 Hot Melt Extruder

ThermoFisher SCIENTIFIC

PharmaLab 16 – Barrel Liners and Screws Removal

Barrel close-up

Barrel open

Barrel liners and plugs removed

All contact parts removed

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Pharma 24 Chill Roll – The Compact Cooling Solution

Flaker parts removed

Belt cartridge removed

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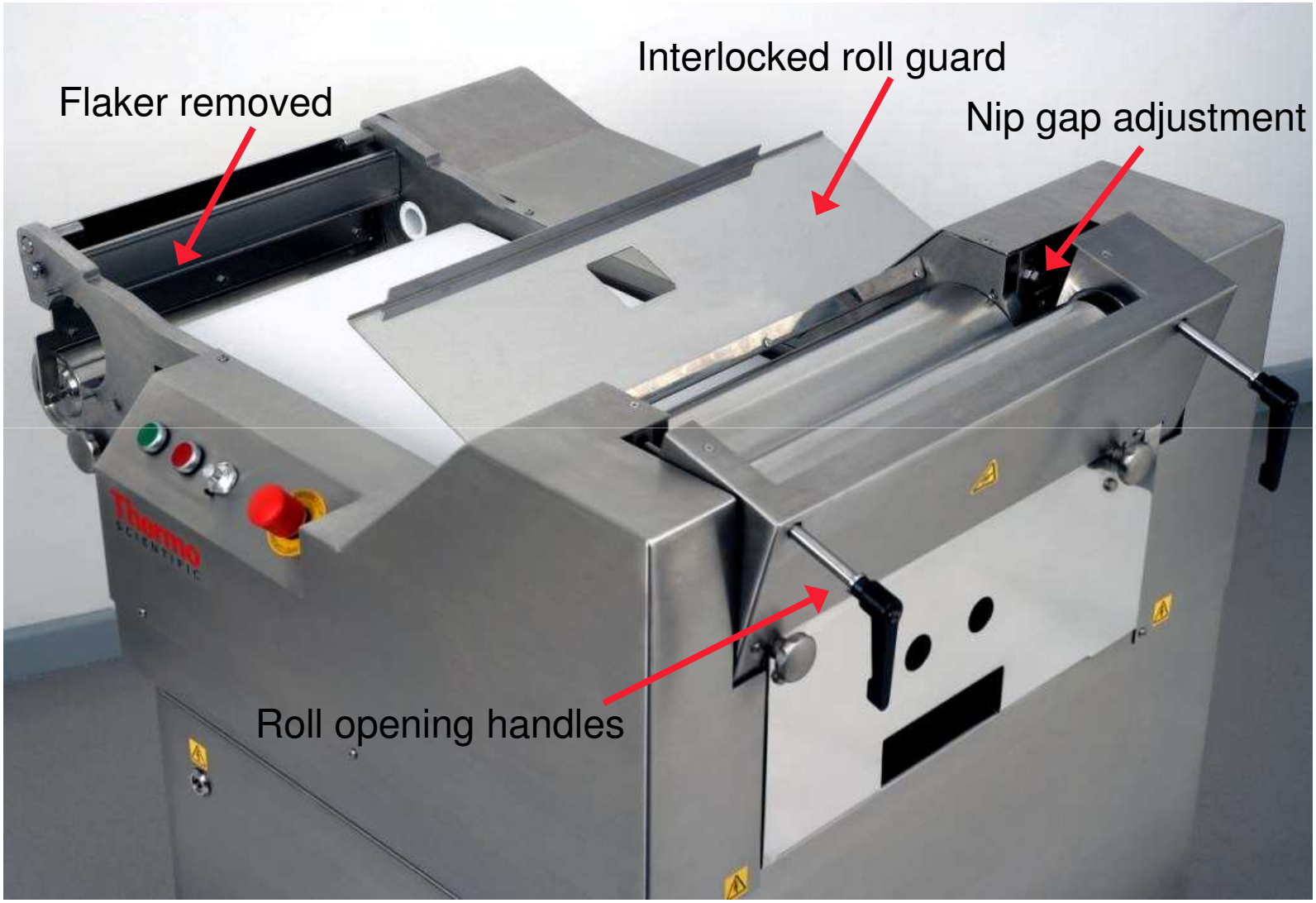
Pharma 24 Chill Roll



Pharma 24 Chill Roll Belt Cartridge

Pharma 24 Chill Roll
Removing the Belt Cartridge.

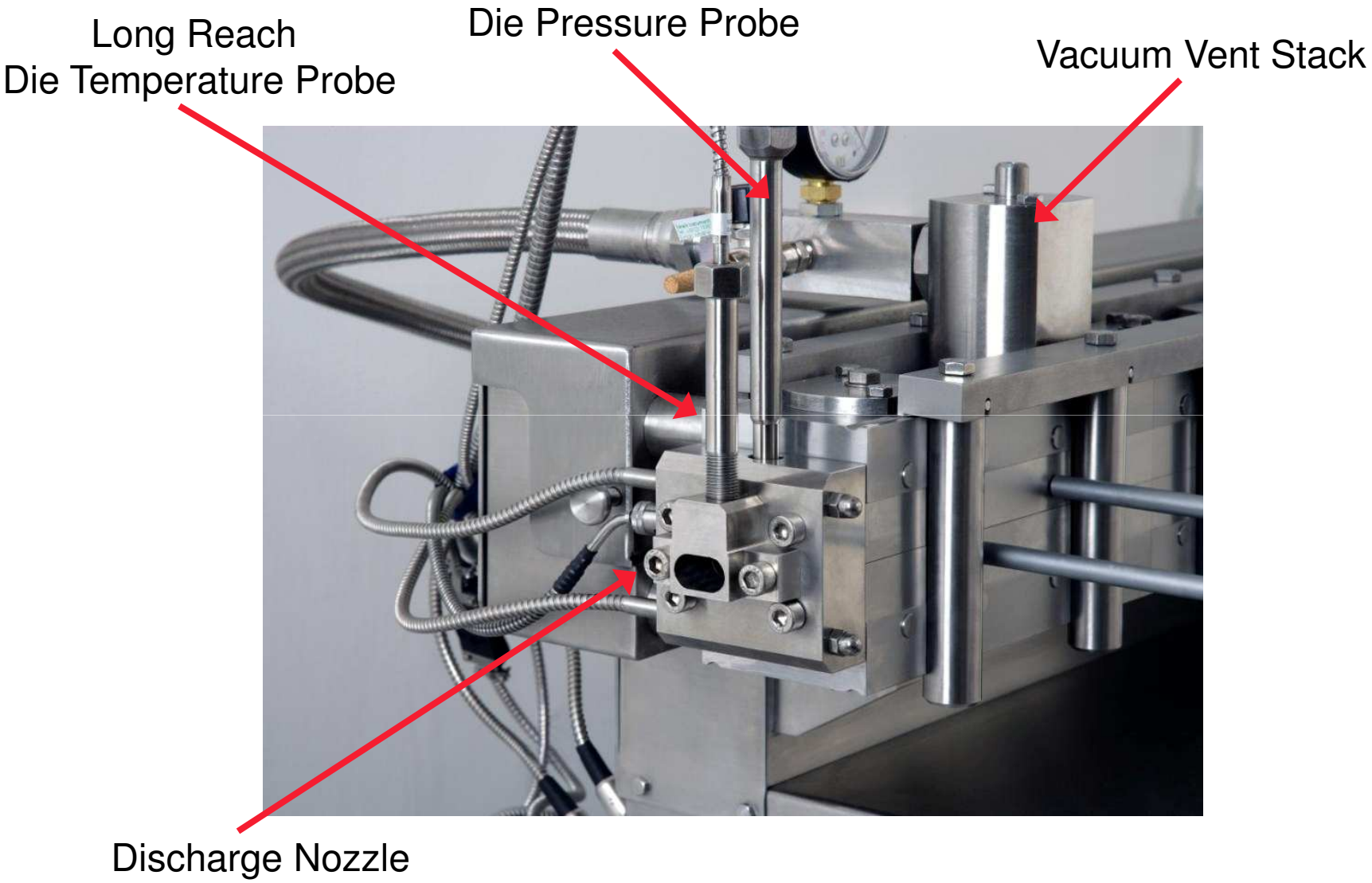
Belt Cartridge removed

Pharma 24 Chill Roll Flaker Cleaning

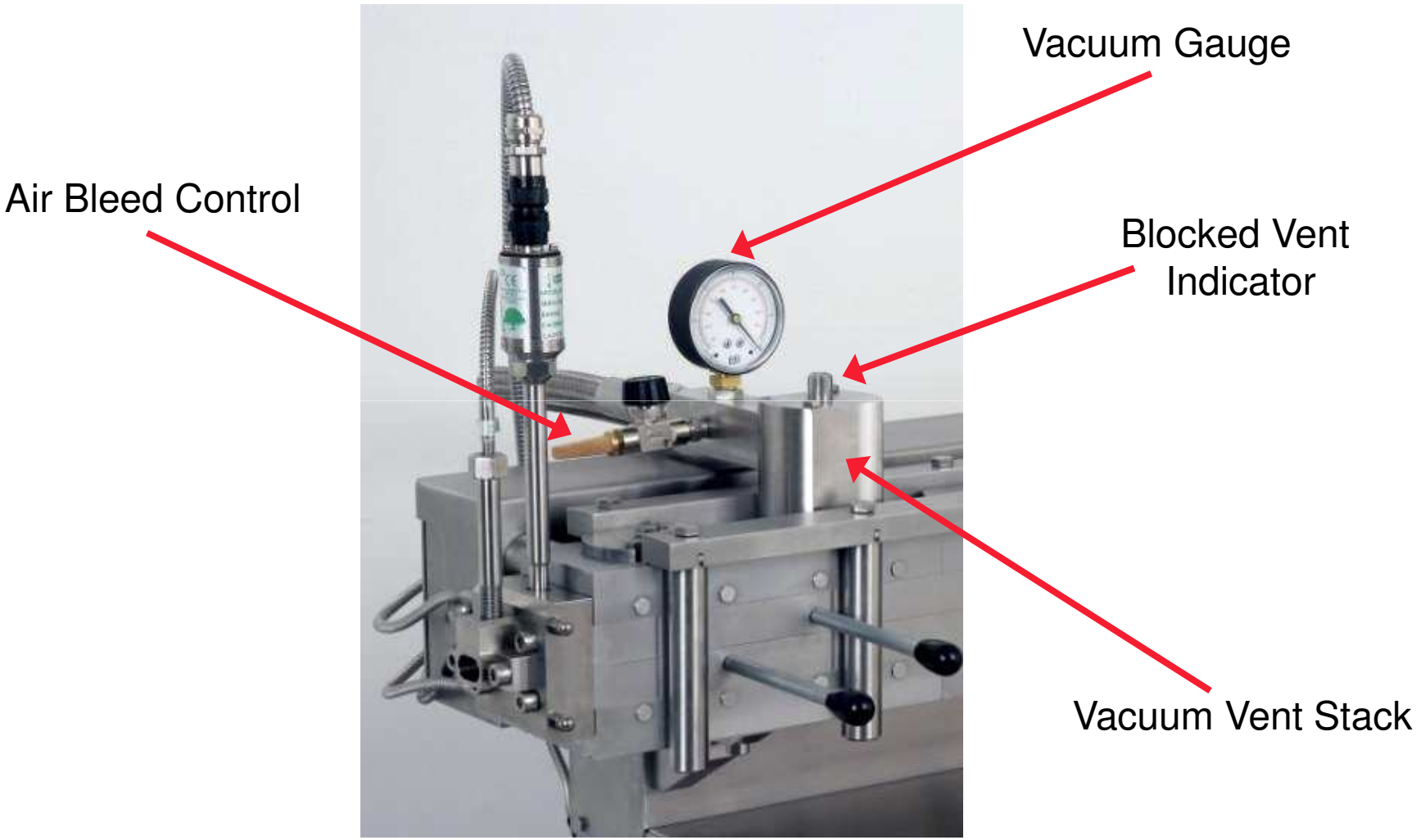
Pharma 24 Chill Roll
(Opening Flaker)

Flaker parts removed

Pharma 24 Hot Melt Discharge Die Nozzle



Pharma 24 Vacuum Venting



Pharma 24 Feeding Solutions

Pharma 16 and 24 Feeder Plattforms

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Pharma 16 and 24 Feeder Arrangement

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Pharma 24 HME Line with Chill Roll

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Introduction TSG

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
    - 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.

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 (Active Pharmaceutical Ingredient) 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*

The Clinical Trials Development Cycle

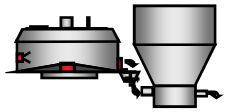
STUDY PHASE	Number of Patients	Duration	Primary Purpose
Phase 1	20 – 100 normal, healthy patients	Up to one year	Safety
Phase 2	Up to several hundred patients	One to two years	Safety and efficacy
Phase 3	Several hundred to several thousand patients	Two to four years	Efficacy and cost benefits
Phase 4 (Post Launch)	Several hundred to several thousand patients	Two to ten years	Cost benefits and outcomes

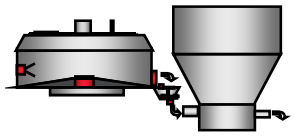
Batch vs. Continuous Granulation

3-10 litre

Phase 1

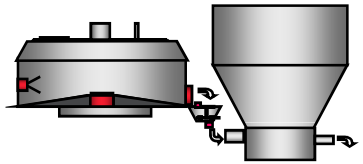
65-150 litre

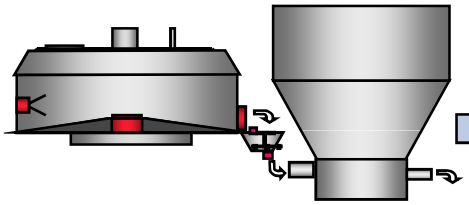




Phase 2

300-600 litre





Phase 3

Pharmalab 16mm

Phase 1

Pharmalab 24mm

Phase 2 **and** Phase 3

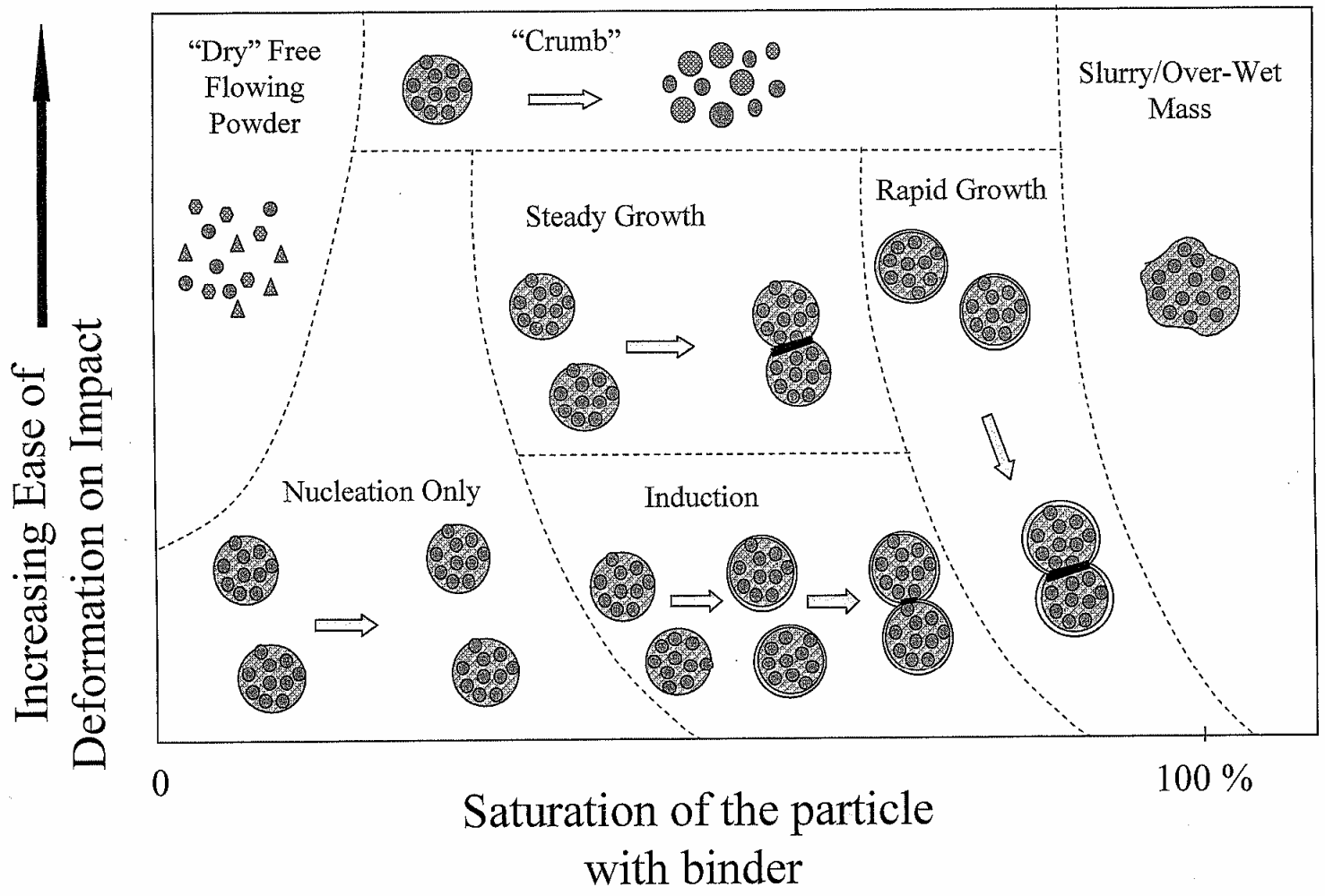
Equivalent Production Capacities

Batch Granulating Equipment	Daily output of Granulate	Continuous Granulating Equipment
65 Litre Batch Mixer 15 kg batch	60 kg Based on 4 batches per 12h day	Pharma 16 TSG 0.2 – 6 kg/h
300 Litre Batch Mixer 75 kg batch	225 kg Based on 3 batches per 12h day	Pharma 24 TSG 1 – 60 kg/h
600 Litre Batch Mixer 150 kg batch	300 kg Based on 2 batches per 12h day	Pharma 24 TSG 1 – 60 kg/h

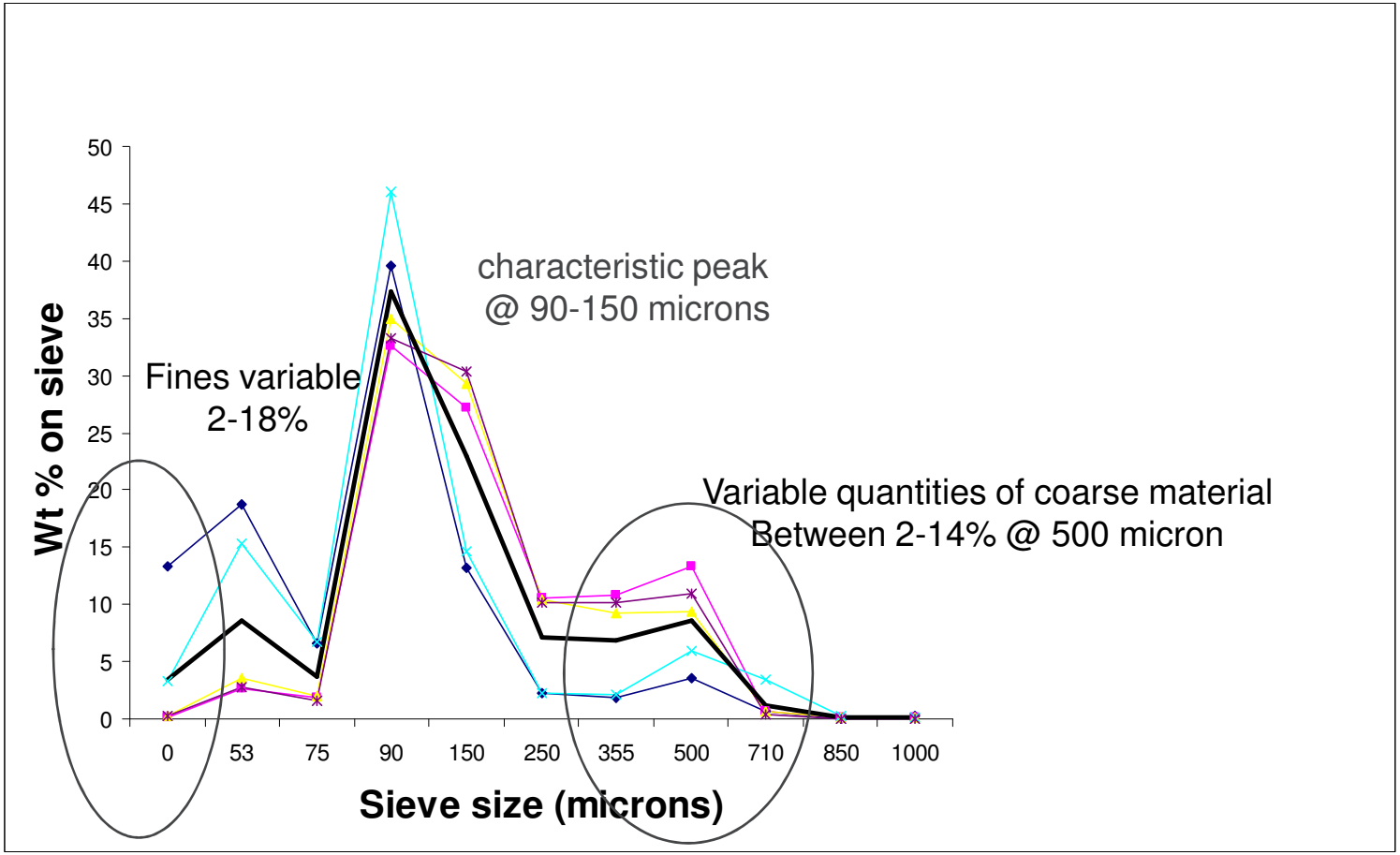
Equivalent Production Capacities

	Equipment Volume				Process Evaluation Samples			Daily Production Rates	
Batch Mixer	Total Tank Volume	Working Volume	Batch Size	Batch Materials Cost	Minimum Sample Size	Number of process samples per Batch	Sample Materials Cost	Batches per day	Typical Continuous Daily (24h) Output
Mixer Size	Litre	Litre	Kg		Kg				Kg
3 Litre	3	1.5	0.75	$750	0.750	1	**$750**	5	**3.75**
10 Litre	10	5	2.5	$2,500	2.500	1	**$2,500**	5	**12.5**
65 Litre	65	32.5	16.25	$16,250	16.250	1	**$16,250**	4	**65**
150 Litre	150	75	37.5	$37,500	37.500	1	**$37,500**	4	**150**
300 Litre	300	150	75	$75,000	75.000	1	**$75,000**	3	**225**
600 Litre	600	300	150	$150,000	150.000	1	**$150,000**	3	**450**
Continuous Mixer	Extruder Free Volume	Maximum Inventory	Minimum Batch Size	Batch Materials Cost	Minimum Sample Size	Number of process samples per Minimum Batch	Single Sample Materials Cost	Output Kg per Hour	Typical Continuous Daily (24h) Output
Screw Diameter	Litre	Grammes	Grammes		Kg			Kg	Kg
Minilab	0.007	3.5	5	$5	0.005	1	**$5**	0.1	**2.4**
Pharmalab 16 25:1	0.068	34	500	$500	0.170	3	**$170**	4	**96**
Pharmalab 16 40:1	0.109	54.5	900	$900	0.273	2	**$273**	4	**96**
Pharmalab 24 25:1	0.228	114	2000	$2,000	0.570	5	**$570**	20	**480**
Pharmalab 24 40:1	0.365	182.5	3000	$3,000	0.913	4	**$913**	20	**480**
Based on:-									
Formulation Density g/ml		0.50			**Formulation** Cost per Kg		$1,000		

Batch Granulation Population Balance

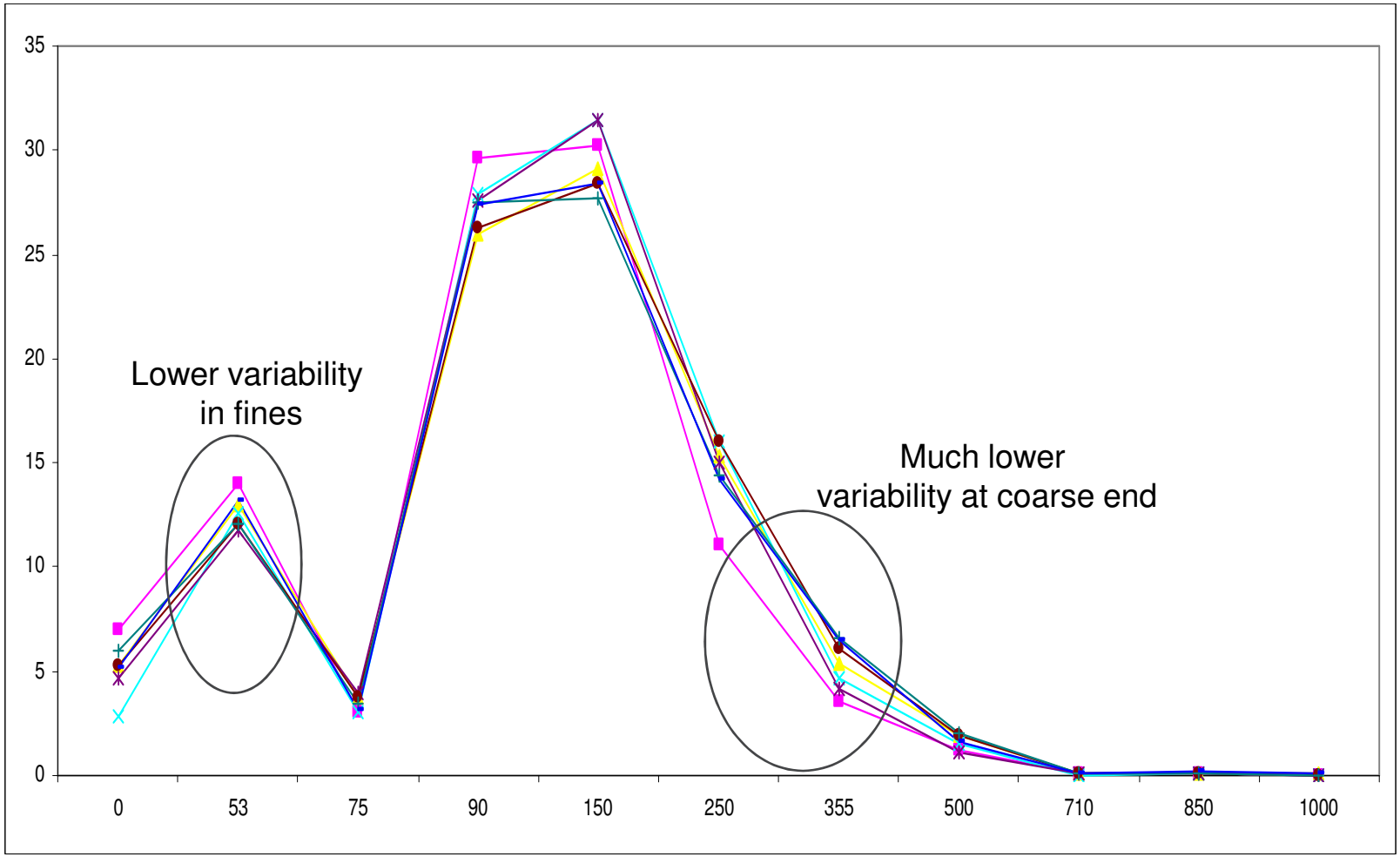


Comparison of materials – example of batch mixed granules



Source ISPE Conference
John Robertson GlaxoSmithkline

Comparison of materials – example of batch mixed granules



Potential for more consistent process !

Source ISPE Conference
John Robertson GlaxoSmithkline

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
  - reduced FTE requirements
  - 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

Product Portfolio TSG

PharmaLab 16 TSG

Gravimetric
Screw Feeder

Liquid Feeding
Pump

Pharma16 TSG
Twin Screw Granulator

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PharmaLab 16 with powder bridge braker

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PharmaLab 16 TSG showing discharge area

PharmaLab 16 TSG dismantled for cleaning

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PharmaLab 24 TSG

Gravimetric
Screw Feeder

Gravimetric
Liquid Feeding Pump

Crammer Feeder

Pharma16 TSG
Twin Screw Granulator

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PharmaLab 24 TSG with feeder platforms

PharmaLab 24 TSG showing barrel clamps

Pharma16 and 24 Feeder Platforms

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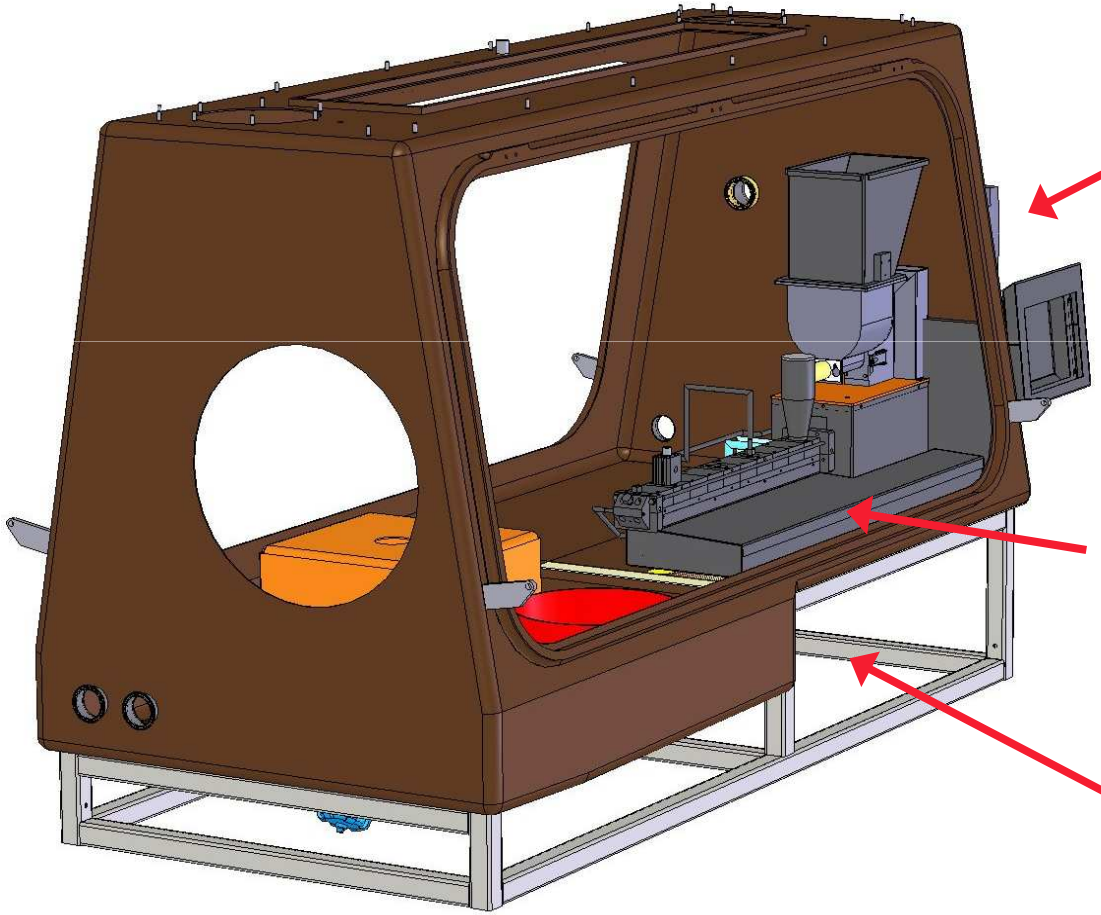
Examples of

Customized Solutions

EuroLab in Isolator

EuroLab extruder and spheronizer in Isolator (Glove-Box)



Motor EuroLab and Feeder outside

Touchscreen outside

Modified extruder base, splash-proof

Electronics integrated in isolator-base

EuroLab in Isolator

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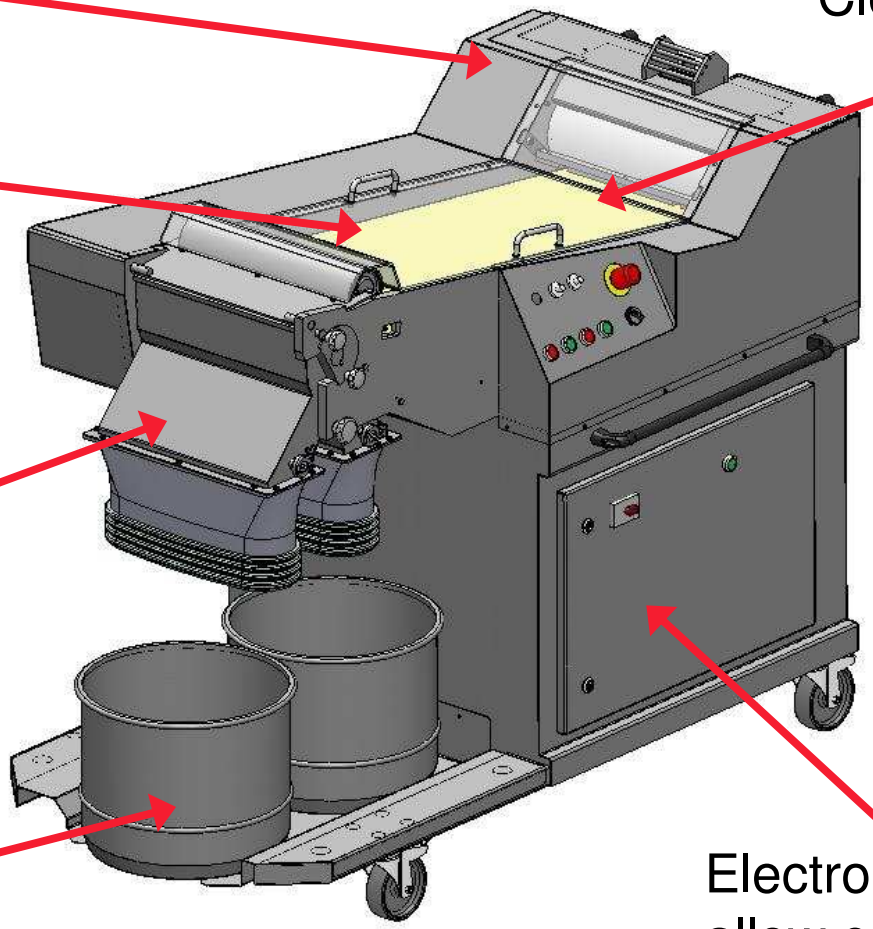
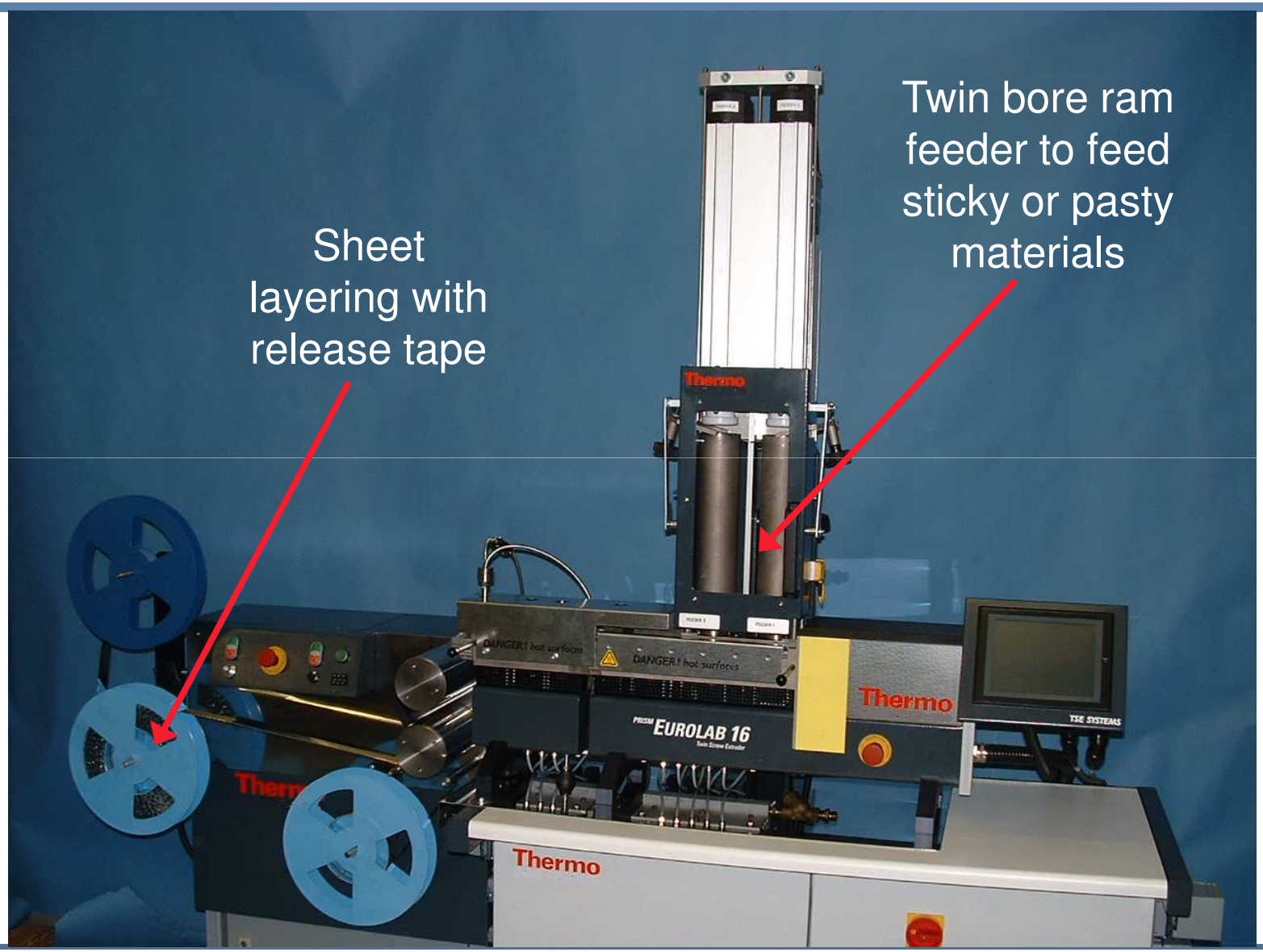
Customized 24 mm Chill Roll



Special Sheet Layering Application



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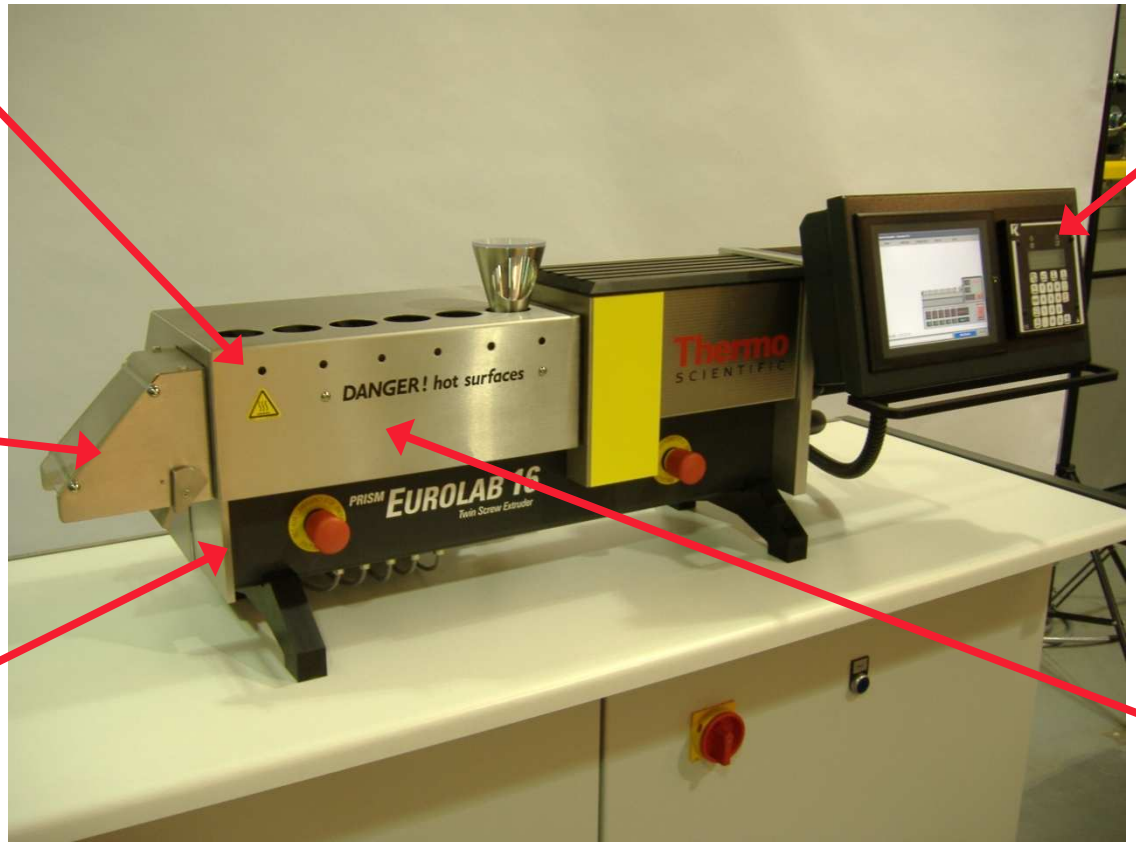
Modified EuroLab with open discharge

Special shroud with acces to feed ports

Integrated feeder control



Open discharge

Active cooling for each zone

Extruder barrel made from pharma grade steel

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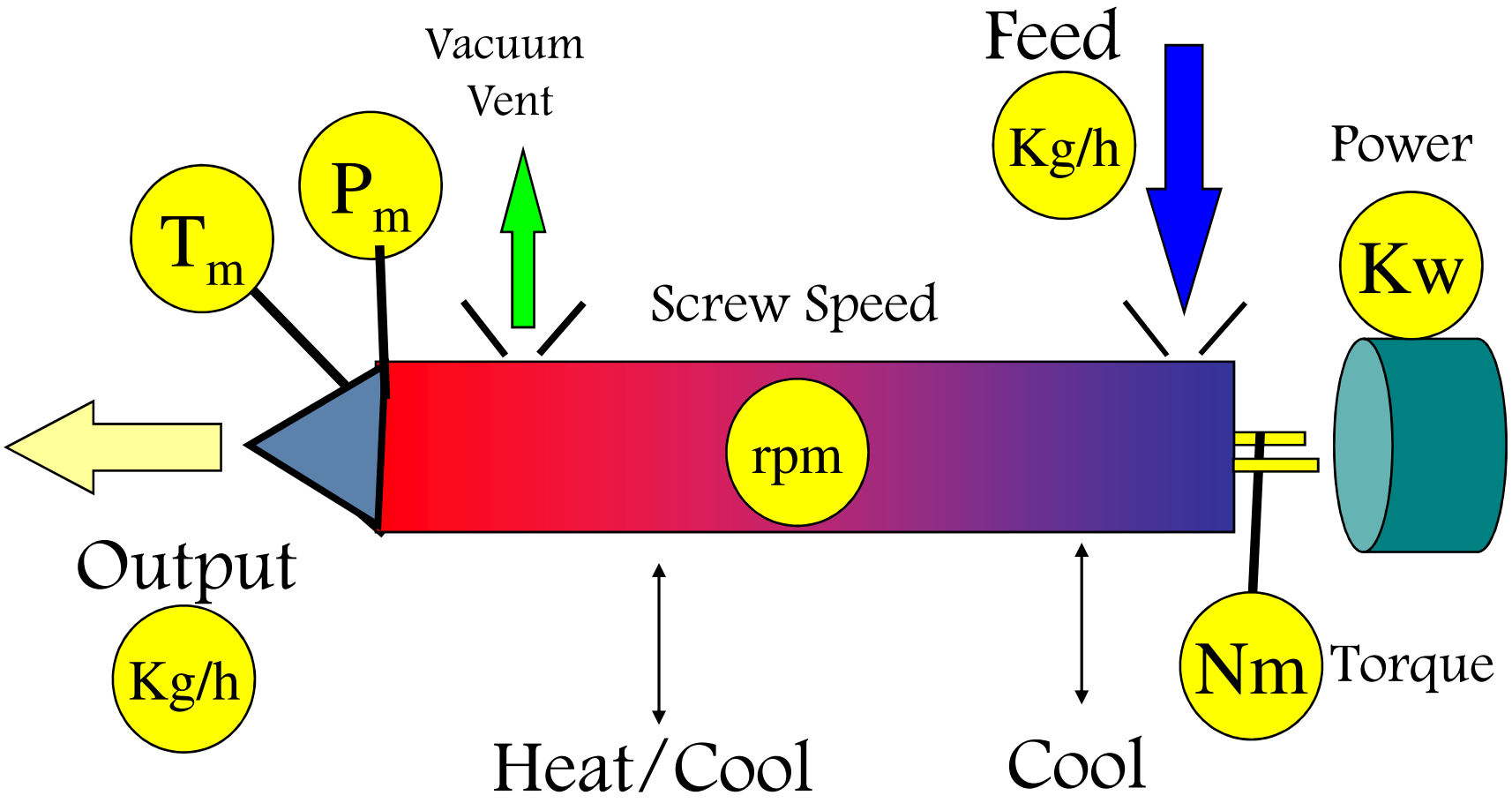
Twin-Screw Compounding

Twin Screw Compounding



Variables in Twin Screw Processing

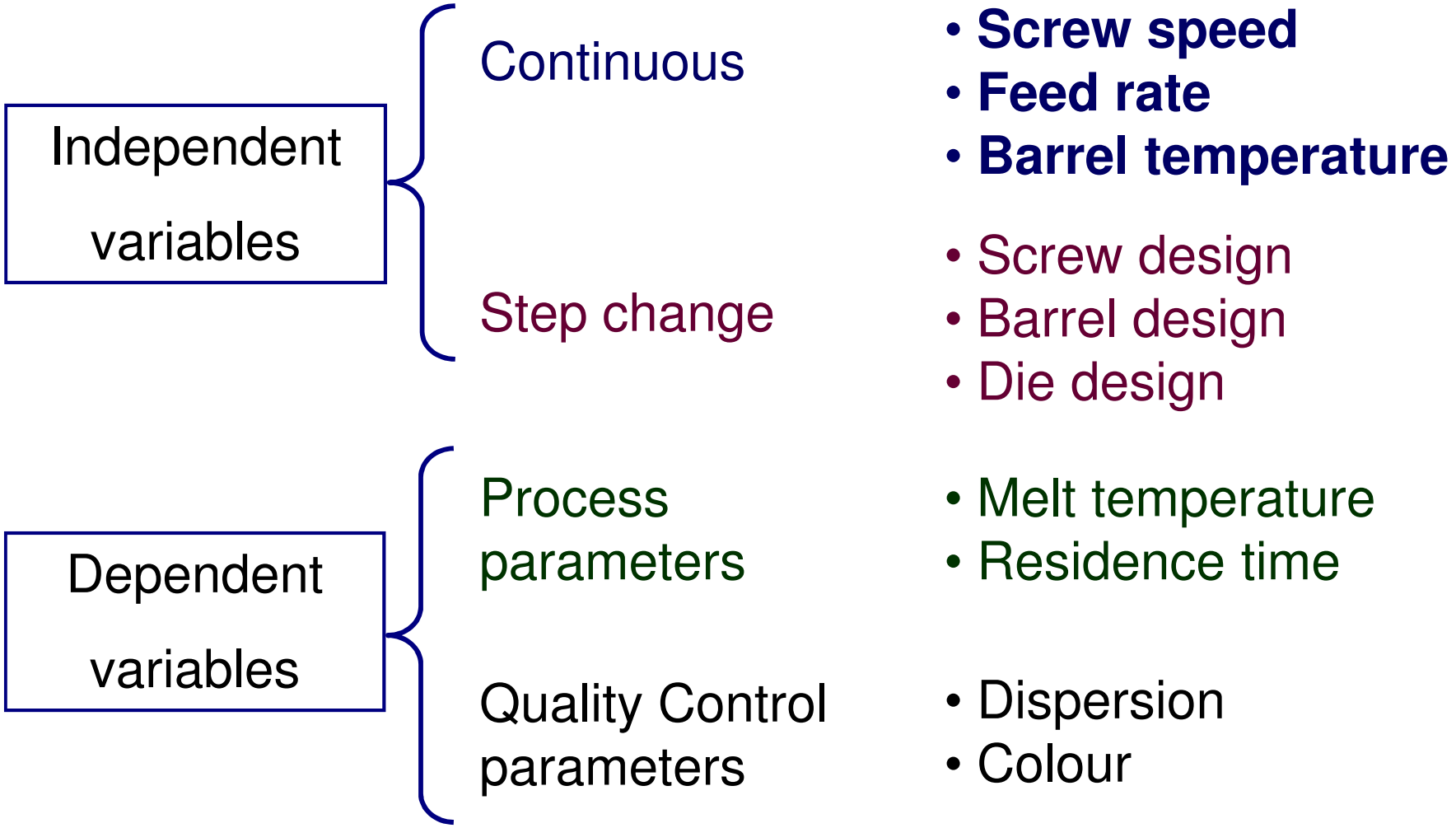
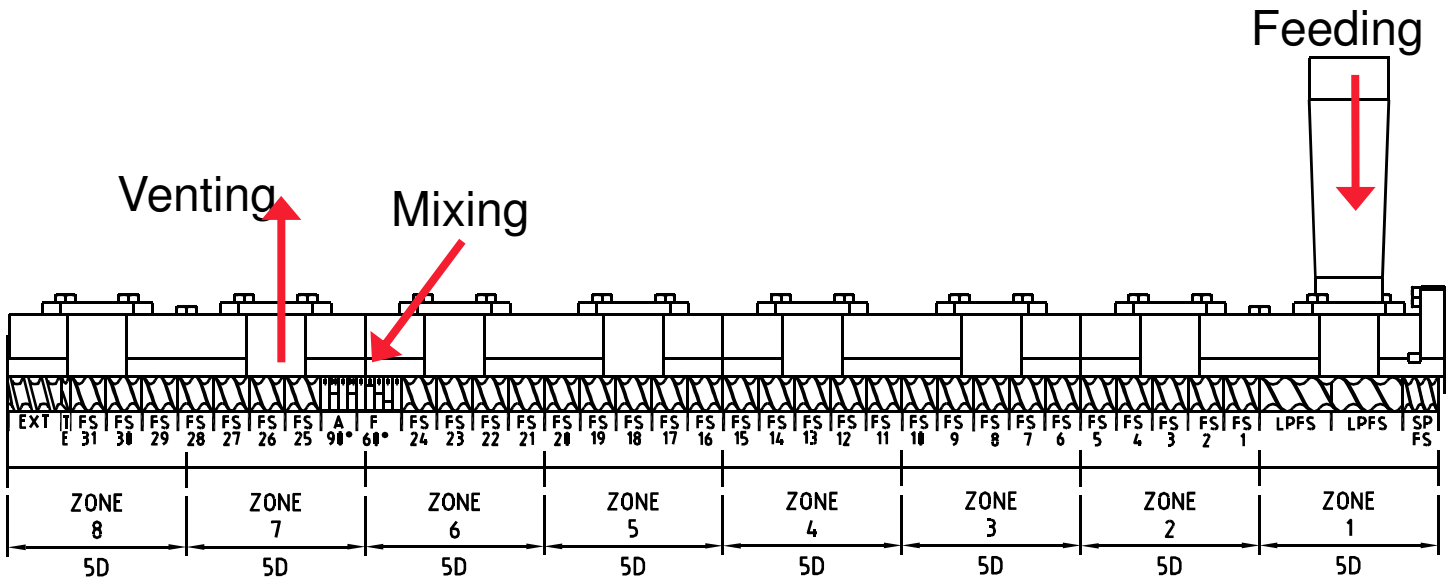
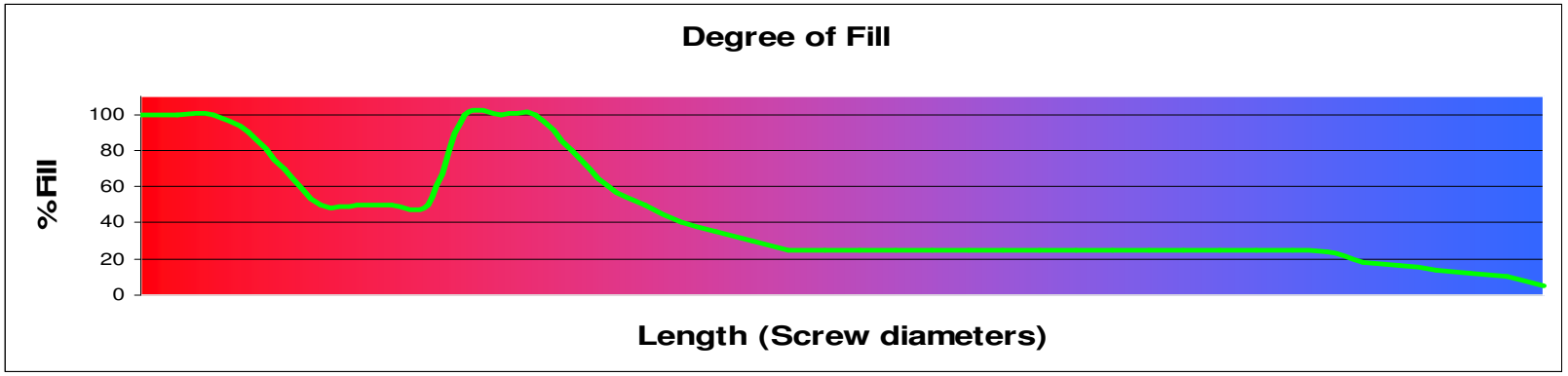


Illustration of degree of fill inside the twin screw.





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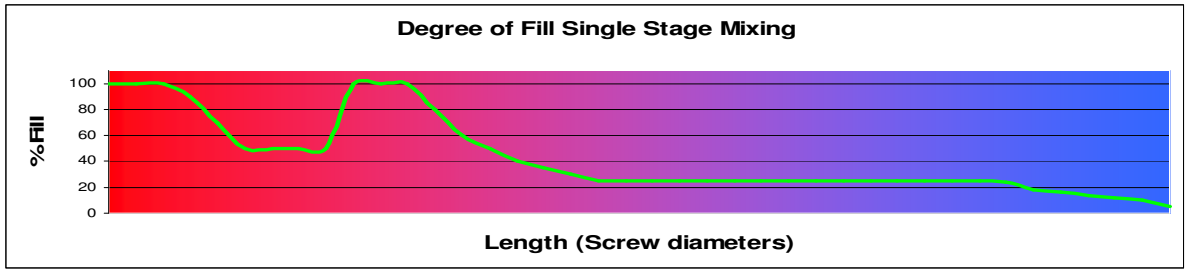
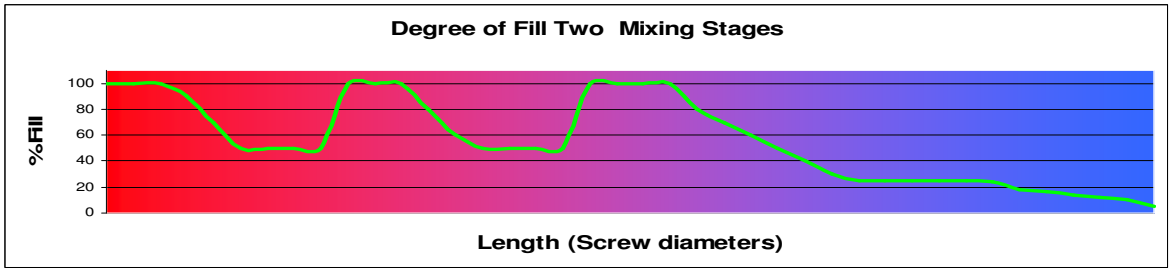
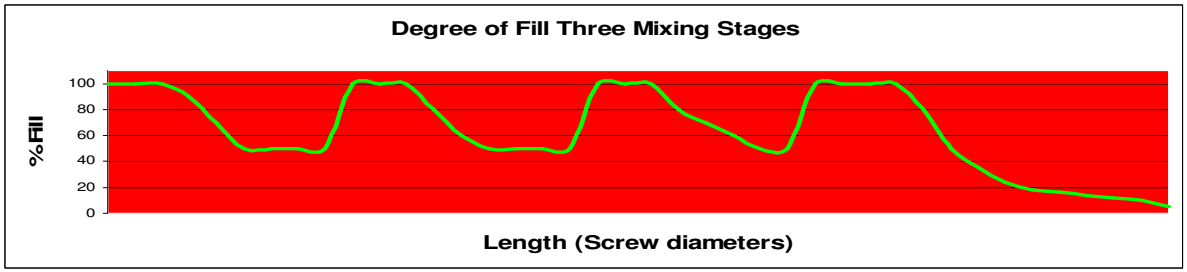
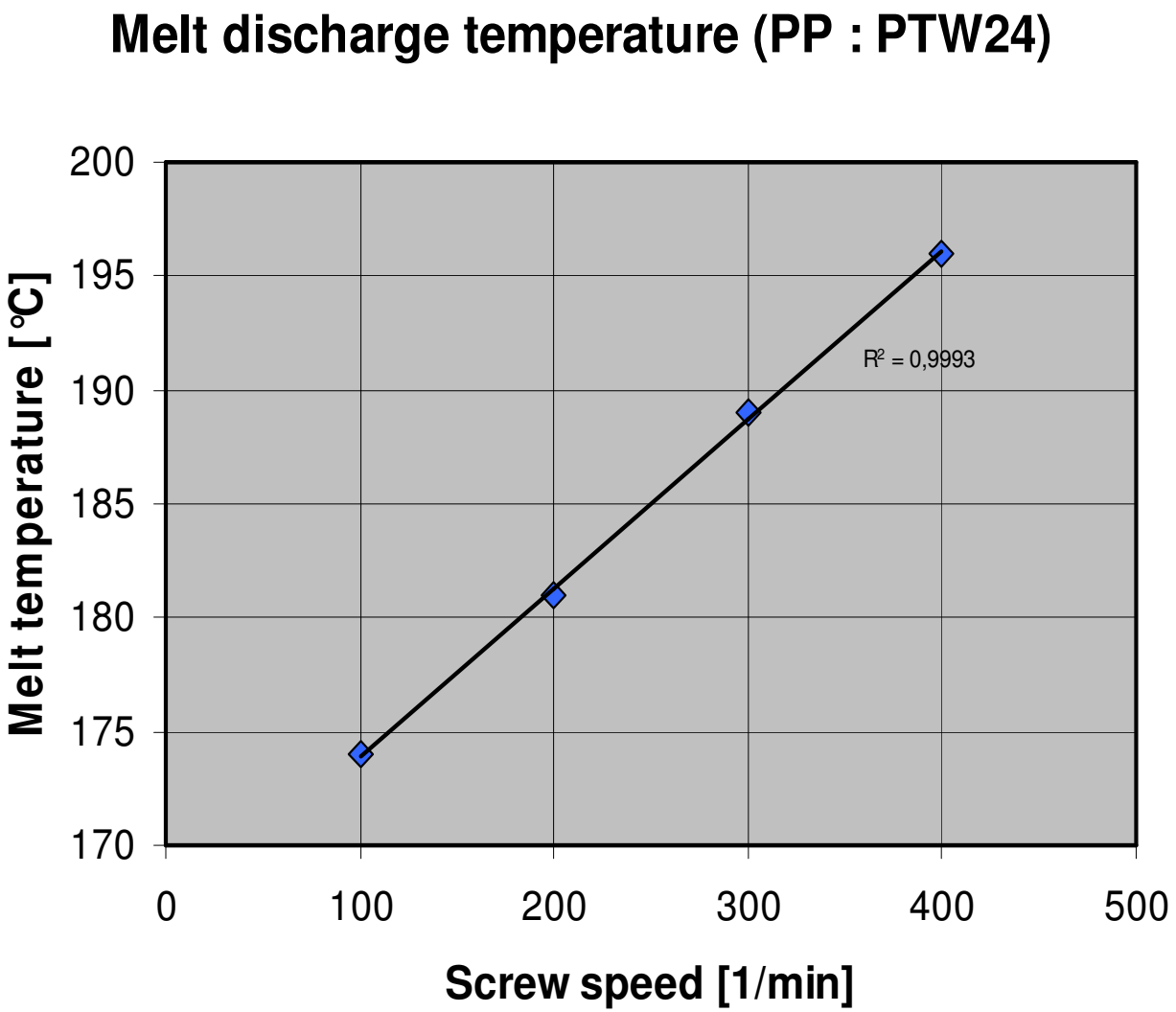
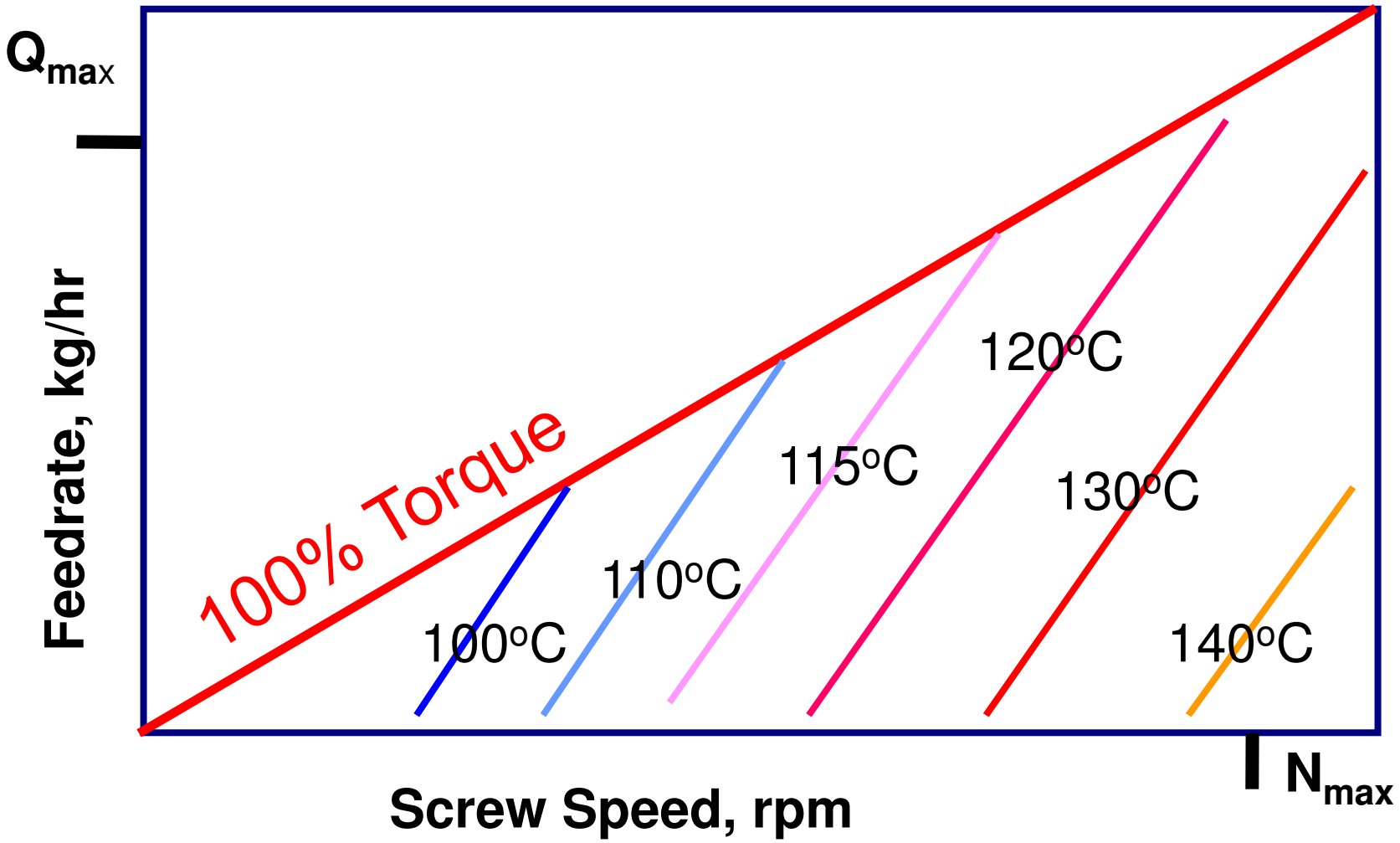
Degree of fill dependent on number of mixing stages.

Residence Time (typical)		Degree of Fill (typical)
60 secs		30%
90 secs		50%
120 secs		60%

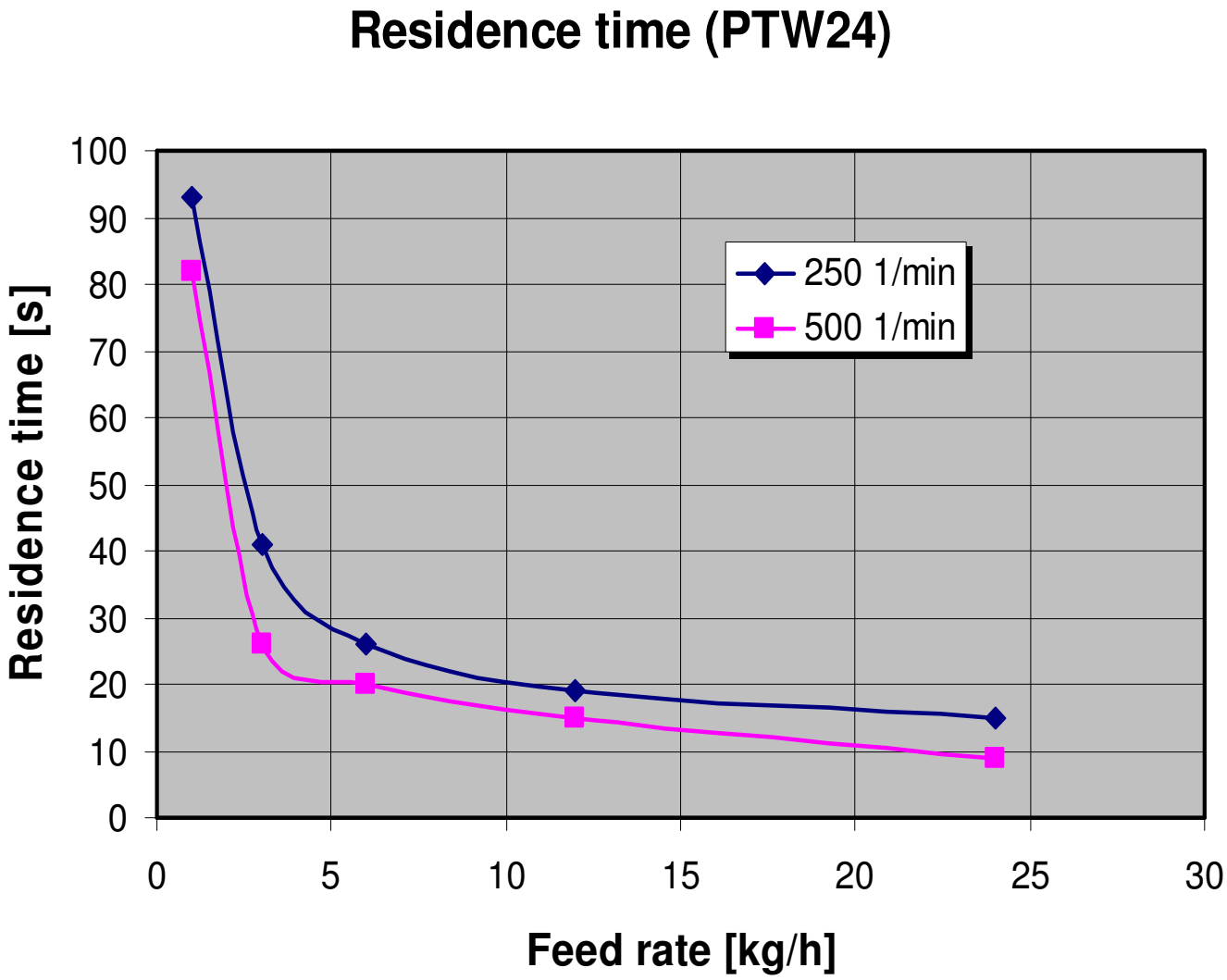
Melt temperature vs. Screw speed



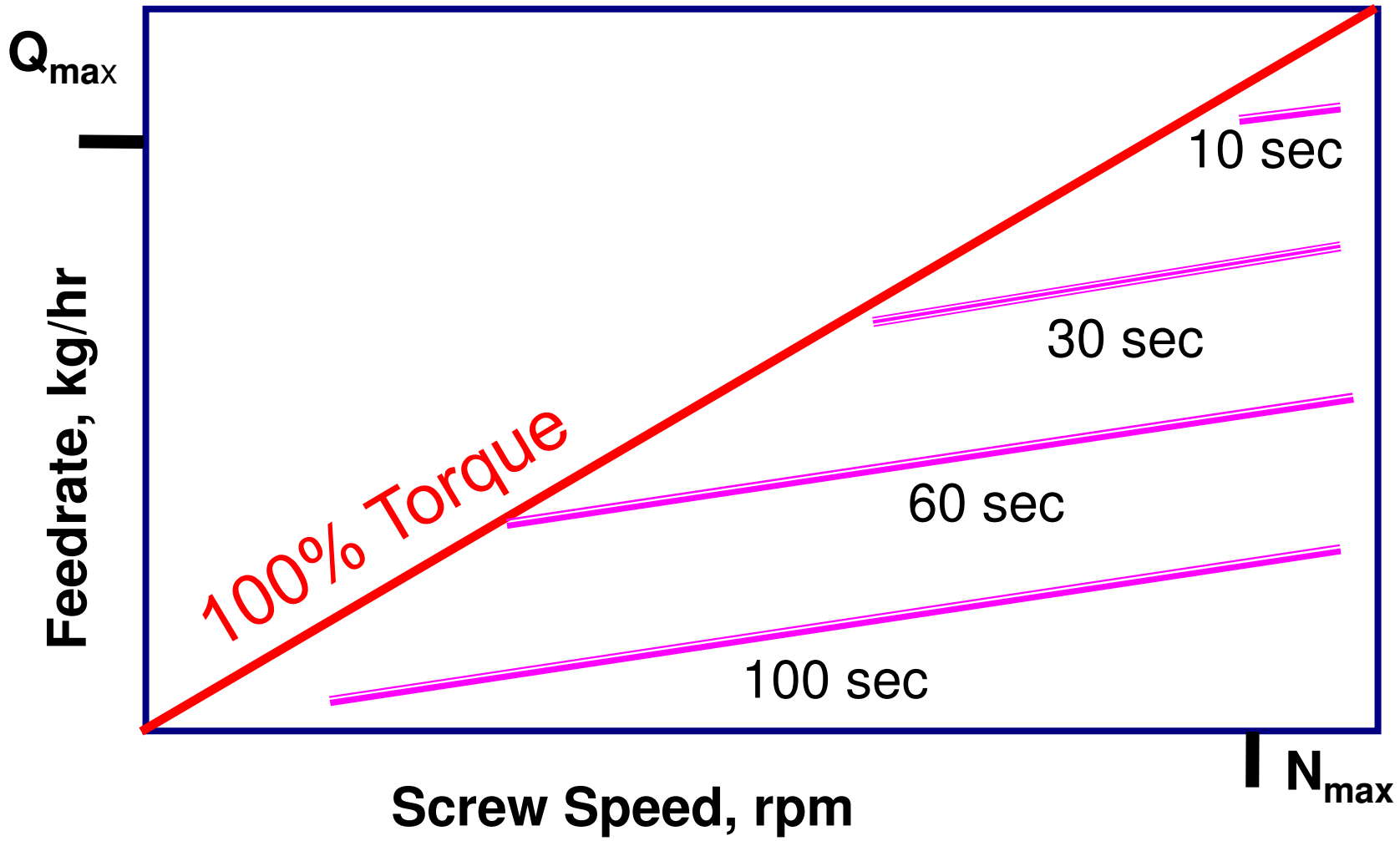
Effect on Melt-Temperature



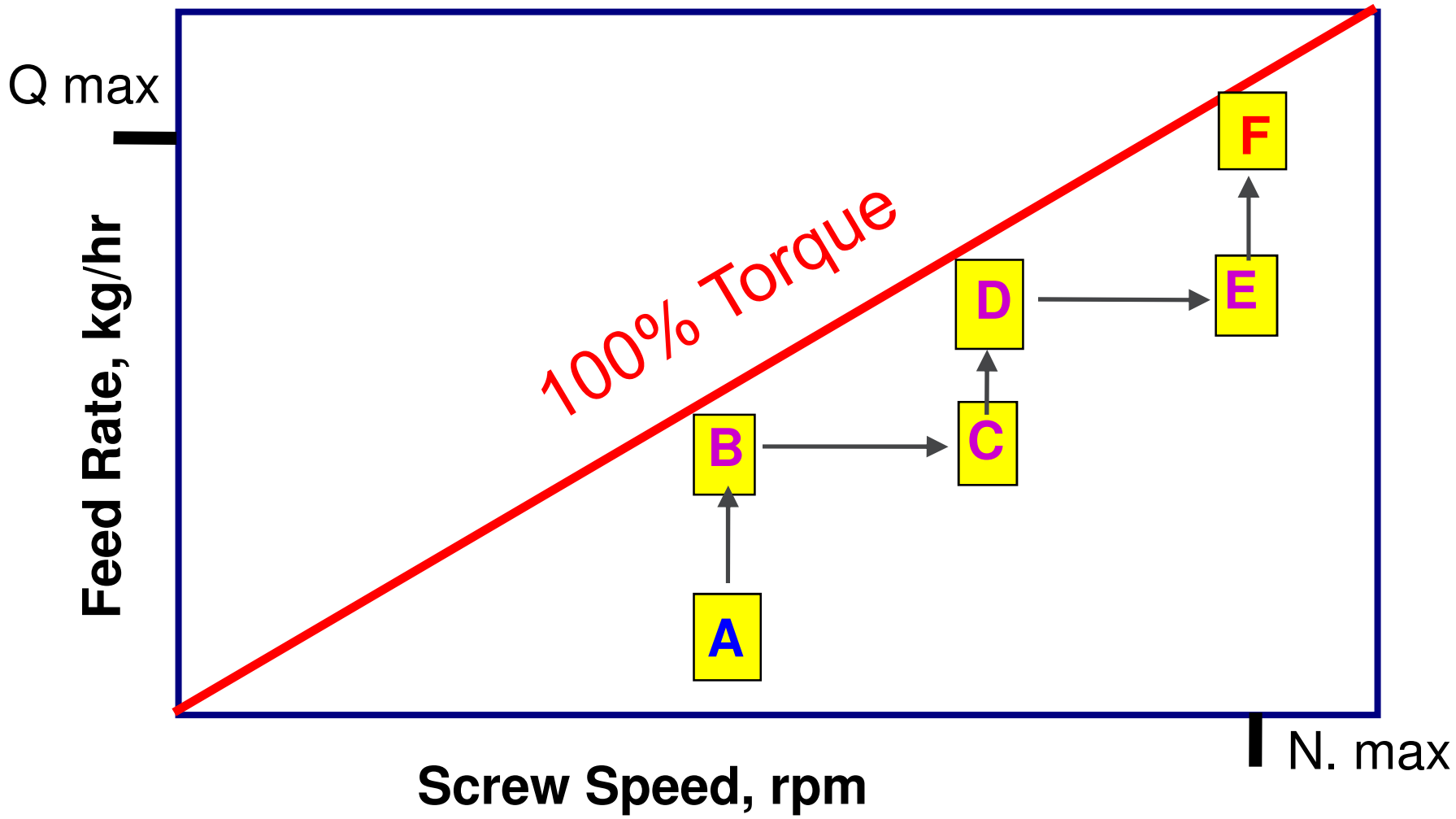
Residence time in a twin-screw



Effect on Residence time



Twin Screw Primary Variables



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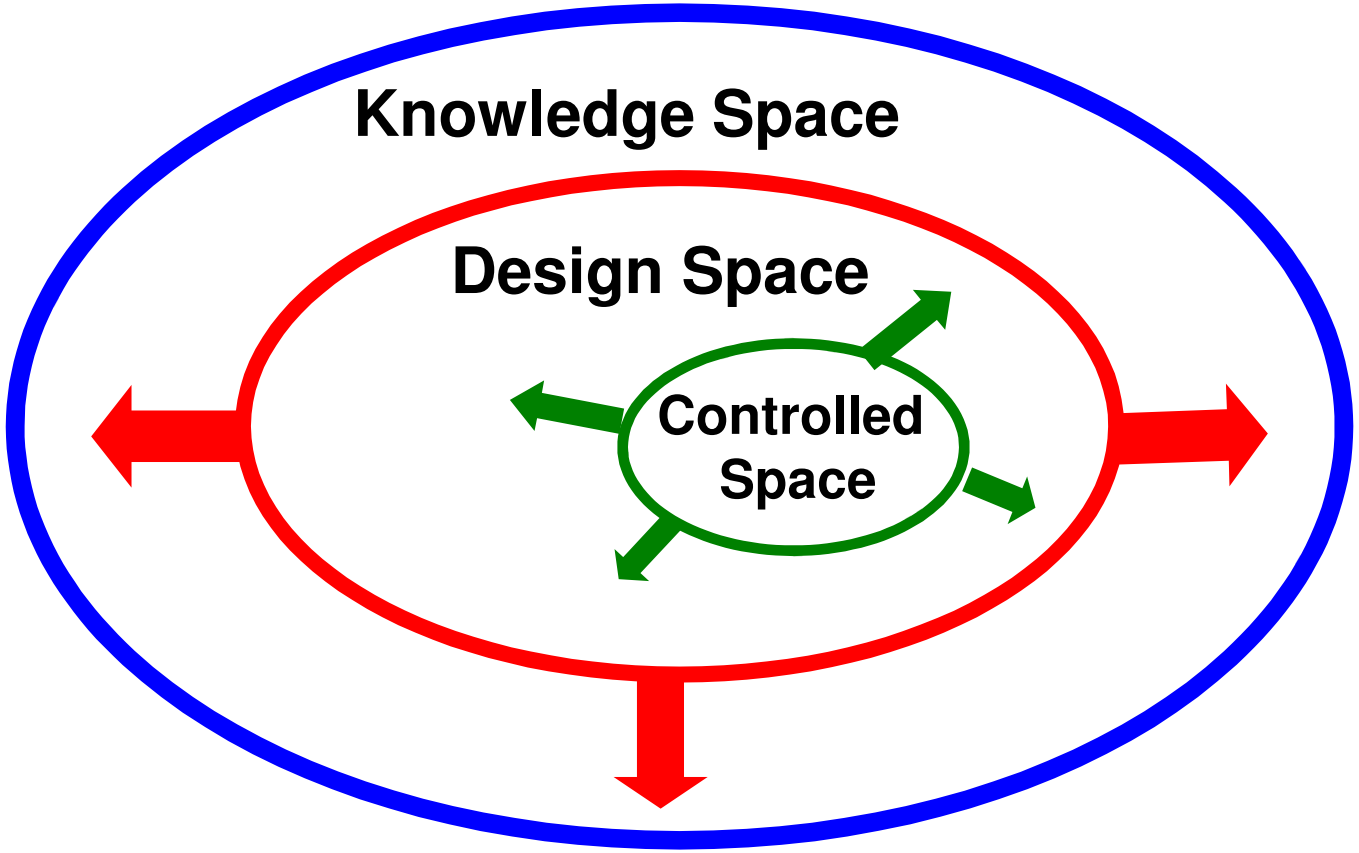
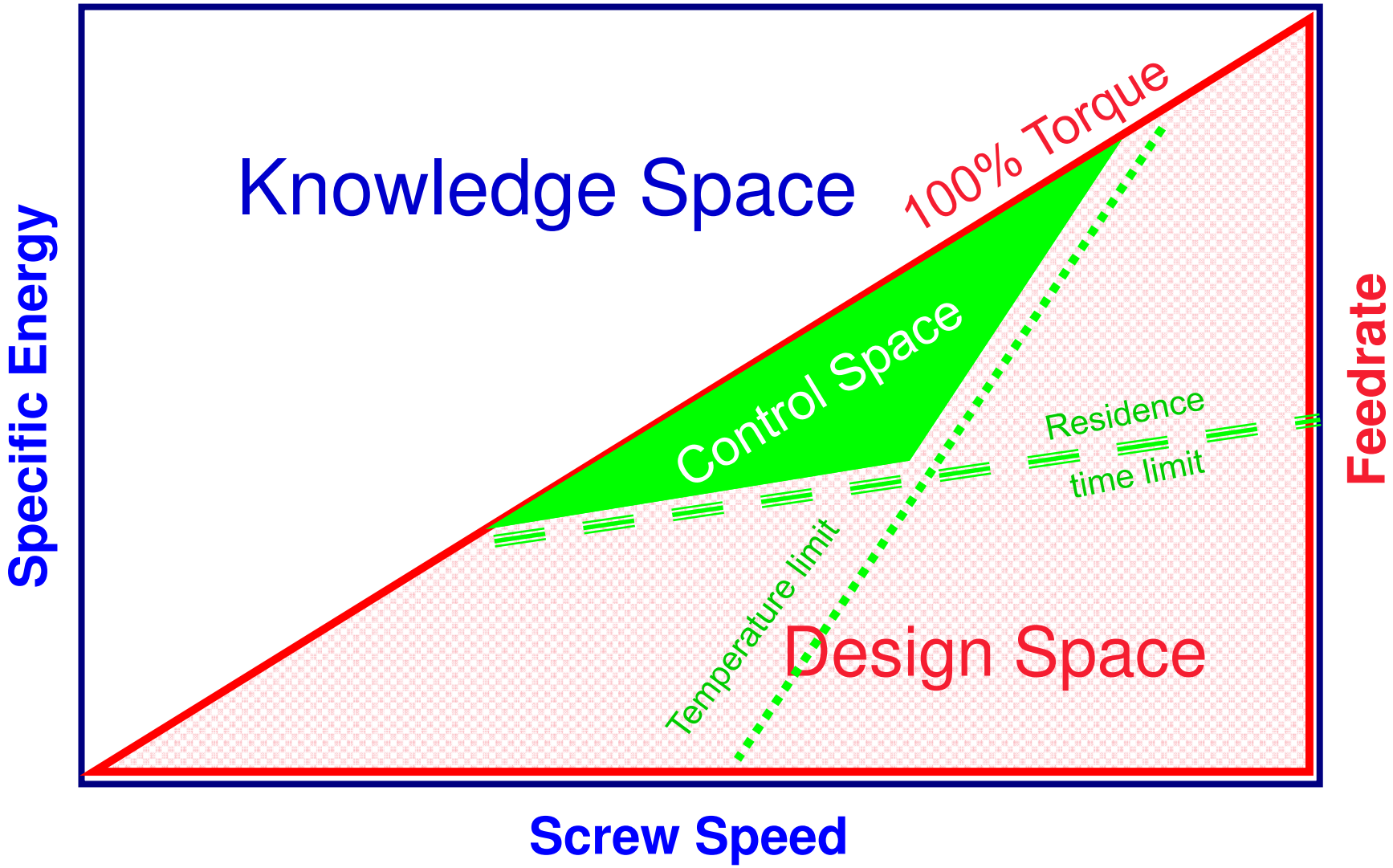
Quality by Design



Quality by Design - Twin Screw Extruders



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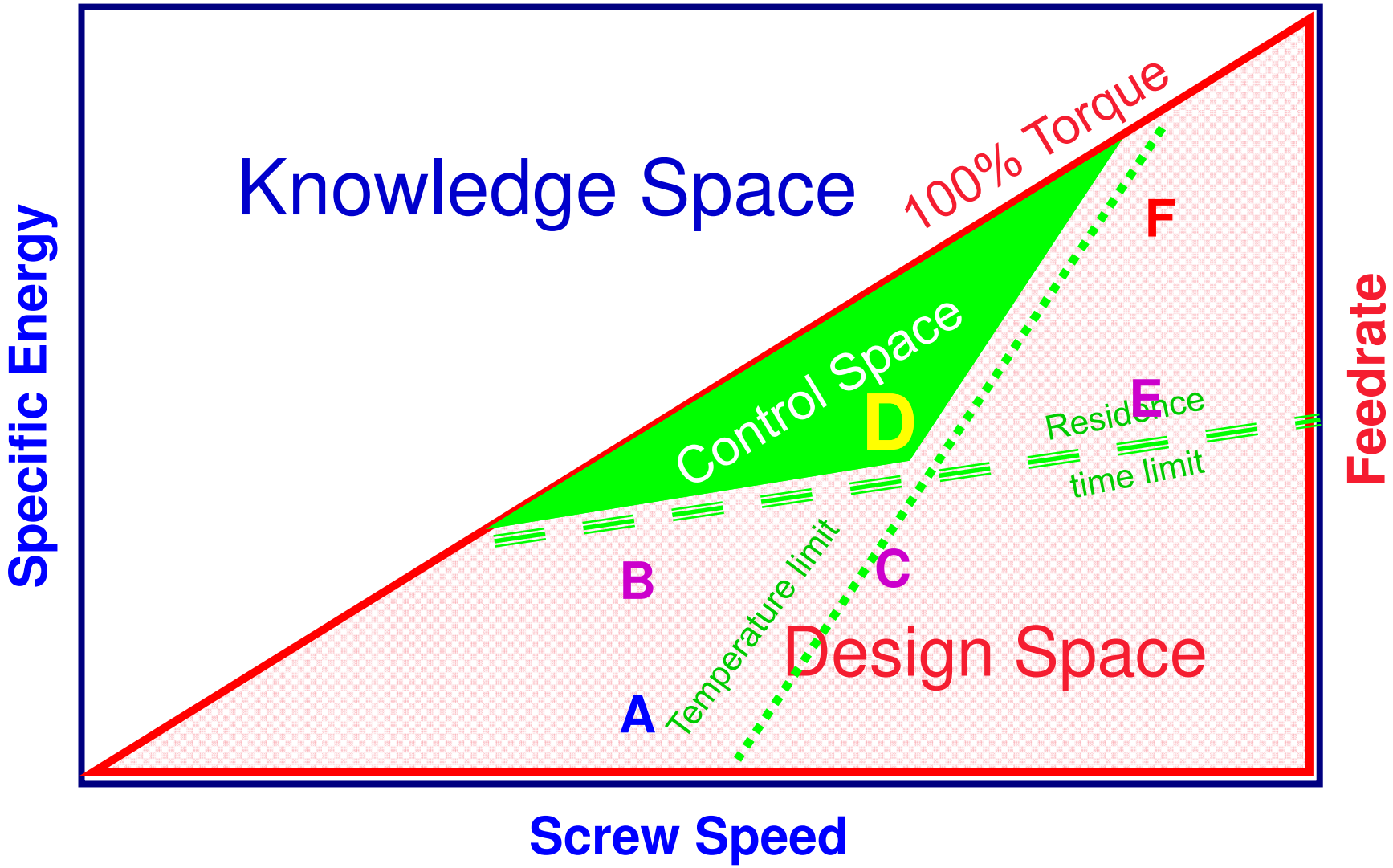
Quality by Design - Twin Screw Extruders



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