Leistritz

LEISTRITZ EXTRUSIONSTECHNIK GMBH

PHARMA EXTRUSION

refreshing extrusion technology

Pioneer in Pharma Extrusion

In the last two decades, extrusion technology has become an interesting alternative to customary manufacturing processes for pellets, tablets or transdermal systems. In this established technology for continuous processing of pharmaceutical masses twin screw extruders are used. An important fact: The FDA encourages continuous processing that supports multi-unit operations (PAT initiative).
Leistritz Extrusion Technology is the technology leader in this area. The company has delivered extruders into the pharmaceutical industry for many years and therefore has extensive know-how.

Basic Principle

The extruder's main task is mixing, homogenising and sometimes also degassing of the material. This is done in a continuous process (extrusion terminology typically refers to a throughput in kg/h). That means: By means of gravimetric feeders each ingredient of a formulation (solid, liquid or gaseous state of aggregation) can be fed into the machine. That way, carrier and auxiliary substances as well as active components can be added into various parts of the processing unit in an exact proportion. Depending on the final product (pellets, tablets, transdermal systems) various extrusion lines can be used.

The extrusion process is suited for:

- incorporating an API into a matrix (i.e. wax, cellulose, starch and further polymers)
- granulation of a tablet premix
- compounding of an antibacterial TPU premix
- stripping off the volatile content from a formulation
- coatings for transdermal applications
- implementation of various dosage forms
- reactive extrusion

Tablets or pellets

Strand cutting

Strand cutting by strand pelletizer or sizing machine (e.g. cutting or cone mill)

Pellets for capsules

Strand forming

Pellets are cooled and conveyed by an air stream in the same equipment, e.g. LMP

Transdermal systems e.g. patches

Final form

Packaging

Main Applications

In pharma extrusion, there are two kinds of processes that need to be distinguished: wet extrusion and hot melt extrusion. In wet extrusion, liquid is fed into a powdery substance. The liquid is used for granulation of the extrudate (material in the extruder) and normally is removed in a later drying phase. In hot melt extrusion, the fluid state is reached by melting the excipient during the process above its glass transition point. After being discharged from the extruder, the extrudate is cooled and thus solidified.

Typical Pharmaceutical Forms

Wet extrusion

Feeding a premix or split feeding the active ingredients and carrier materials

Mixing, homogenizing **Extruder**

Strand shaping

Shaping of the extrudate by discharging via a die head

Strand cooling by air-cooling on e.g. belt, vibration or spiral conveyors

Strand cooling

Melt extrusion

Feeding a premix or split feeding the active ingredients and carrier materials

Melting, mixing, homogenizing, dispersing **Extruder**

Strand shaping

Shaping of the extrudate in cylindrical shape by discharging via a die head

Strand cutting directly after discharge of the extrudate „hot face" by a "hot face pelletizer"

Strand cutting

Feeding a premix or split feeding the active ingredients and carrier materials

Melting, mixing, homogenizing, dispersing **Extruder**

Shaping

Shaping of the extrudate into a film or strip via a flat film die

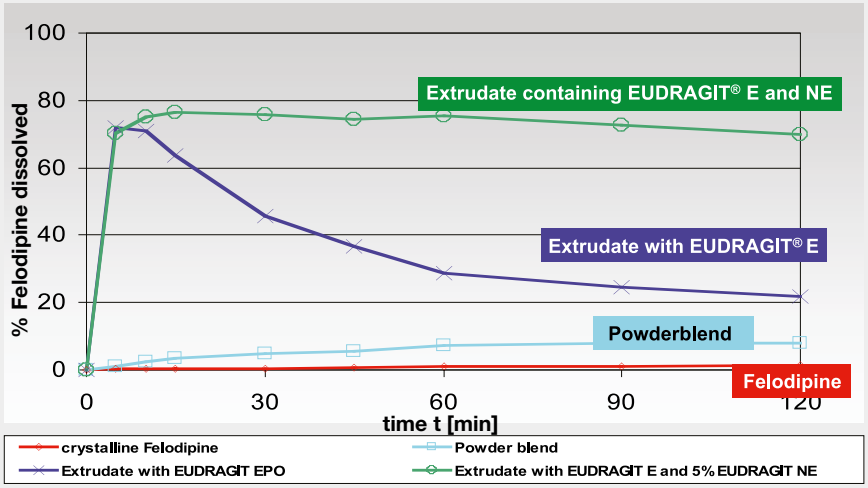
Direct forming and cooling in a calender system

Forming and cooling

The main advantages of hot melt extrusion are:

enhancement of solubility

EUDRAGIT® NE as precipitation inhibitor



Verapamil·HCl Tablets

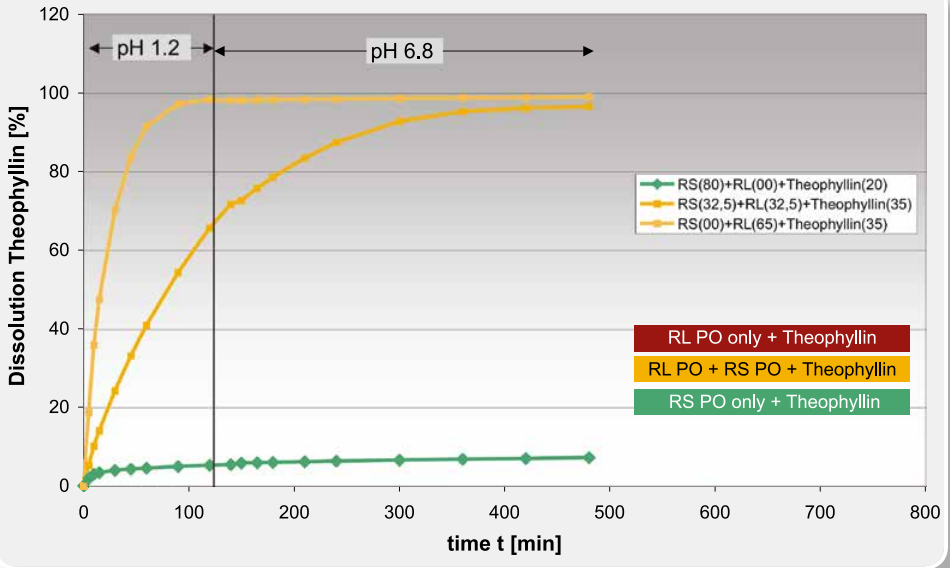
	Bitterness Value* Verapamil·HCl = 100	Granules 10 pcs. in mouth	Tablets 80 mg Verapamil·HCl
EUDRAGIT®L 100-55 : Verapamil·HCl 50 : 50 w/w	10	30s	10s / 20s
Preparation 4135 F* : Verapamil·HCl 50 : 50 w/w	10	30s	10s / 20s

* = milled compound

no bitter taste | slightly bitter taste | bitter taste

taste masking

sustained release

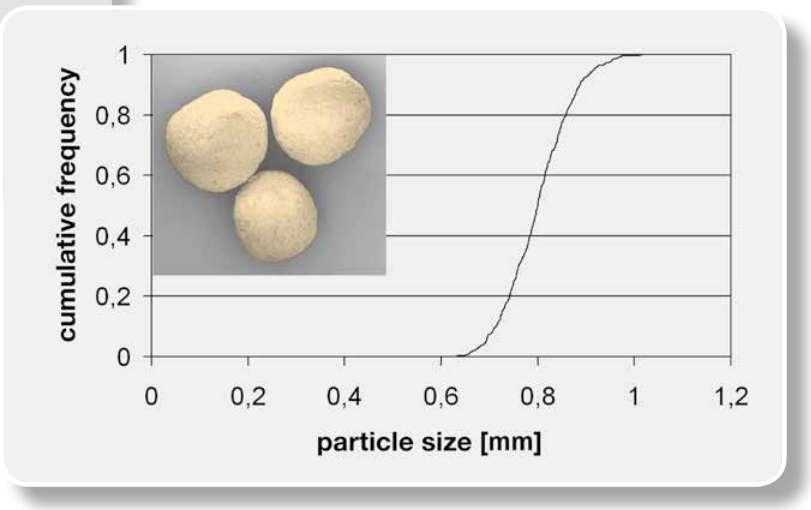


- stability of the formulation (in relation to the processing technique)
- little use of additives
- efficiency of production
- process free of solvents

source: Evonik

The main focus in wet extrusion is on

- production of granule particles for functional coatings
- spherical particles
- small particle size distribution
- controlled drug release
- uniformity of drug content
- easy processing by means of continuous granulation and online monitoring
- batch size adaptation by changed processing times



source: Heinrich-Heine-University, Düsseldorf

Process Technology when Manufacturing Solid Pharmaceuticals

Advantages of the continuous extrusion process compared to established batch processes:

- homogenous mixing efficiency
- self-cleaning/self-emptying of the extruder screws
- easy automation and control
- easy scale-up → reduction „time to market“
- short product change cycle
- reliable reproduction of formulation quality
- single stage processing (incl. shaping of the pharmaceutical form)
- low operating and investment costs

Benefits for the product:

- short residence time and small range of residence time distribution
- high throughput
- small particle size distribution
- high dosing of active agent possible
- low material content in extruder at a high throughput
- dosing of several components (solids, fluids and suspensions) possible, i.e. the extrusion line also ensures correct implementation of formulation valves
- possibility of adding fluid into the running process

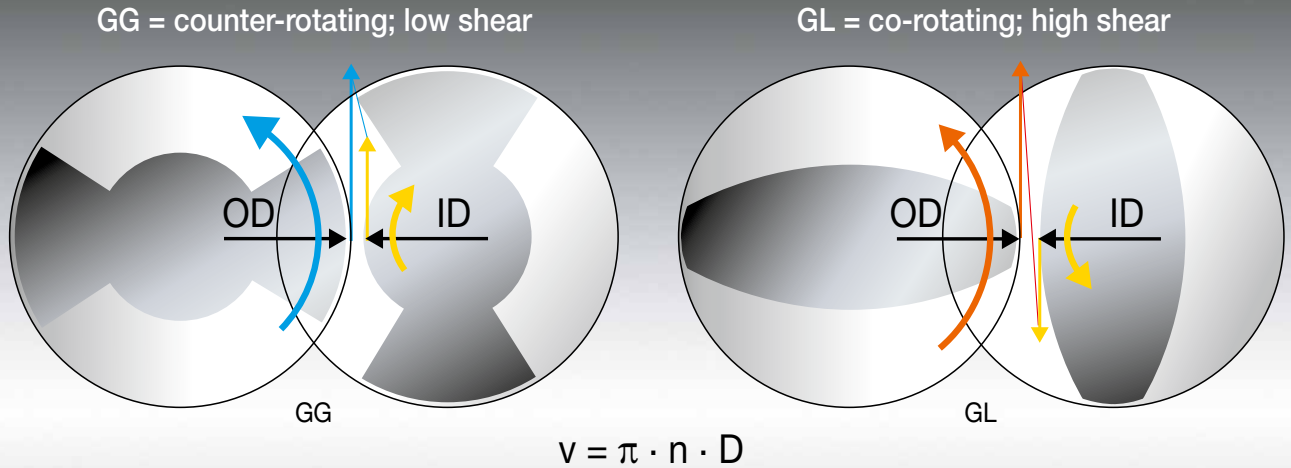
Extruder Engineering

Two types of extruders can be used in the pharmaceutical industry: the single screw and the twin screw extruder. Single screw extruders are the simplest extrusion system worldwide. The principle: One screw, which by means of various screw geometries facilitates various processes, rotates inside the barrel. As the name implies, two screws are used for operation in the twin screw extruder. The screws either rotate in the same direction (co-rotating) or in the opposite direction (counter-rotating).

Advantages of twin screw extruders (co- and counter-rotating) compared to conventional manufacturing techniques:

- melting properties
- very good mixing effect - homogenizing of the product
- self-emptying due to second screw (defined residence time possible)
- high shear rate in order to crush agglomerates
- sealed off processing section to prevent cross-contamination
- short processing time
- integration of several process steps in one machine
- little space required (yet with the same production capacity)
- trouble-free scale-up to production scale (transfer of lab results to production size)
- flexible screw geometry and segmented barrels
- exact temperature control
- higher throughput

Distinction between counter-rotating and co-rotating twin screw extruders

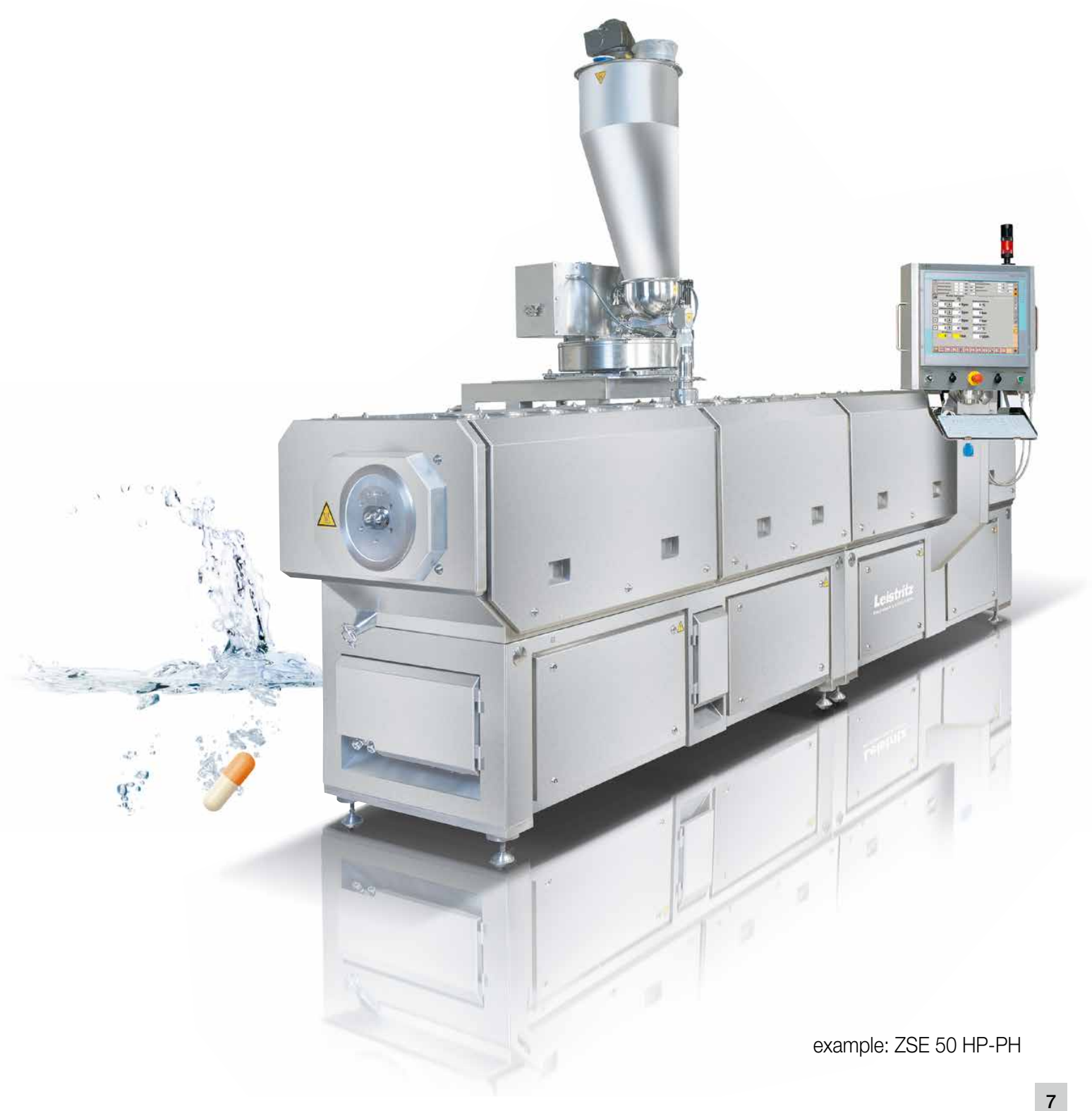


The tightly intermeshing screw profile of co-rotating twin screws provides an immensely significant effect: **self-emptying**. By means of a high shear rate created in the gap between the screws, they clean each other out. The extruder discharges the material automatically.

Extrusion Lines in GMP Design

For the special demands in the pharmaceutical industry, Leistritz presents an extruder series including according auxiliary equipment in GMP design.

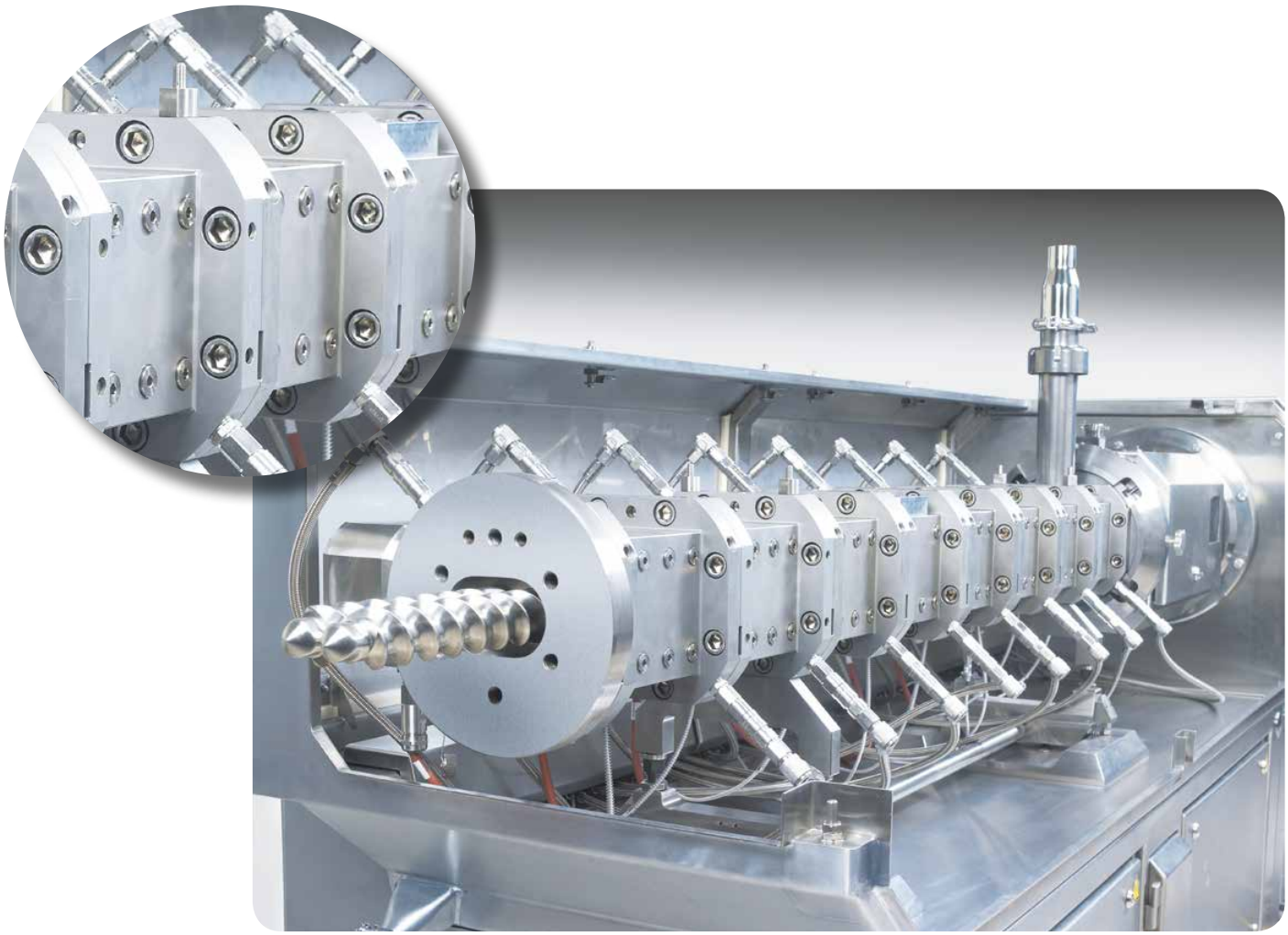
Extruders for pharmaceutical applications are characterized not just by visible features like the usage of stainless steel. This machine generation provides everything that meets the GMP requirements of the industry: special fittings, material combinations, surface textures and an increased documentation for qualification. The extrusion lines have an outstandingly detailed design for all components with respect to cleaning, excellent process stability to ensure continuous product quality, an optimal process control, and complete documentation.



example: ZSE 50 HP-PH

Processing Unit - the Heart of the Extruder

The processing unit consists of screws and barrels, which are manufactured from highly alloyed steels as they are in direct contact with the product.



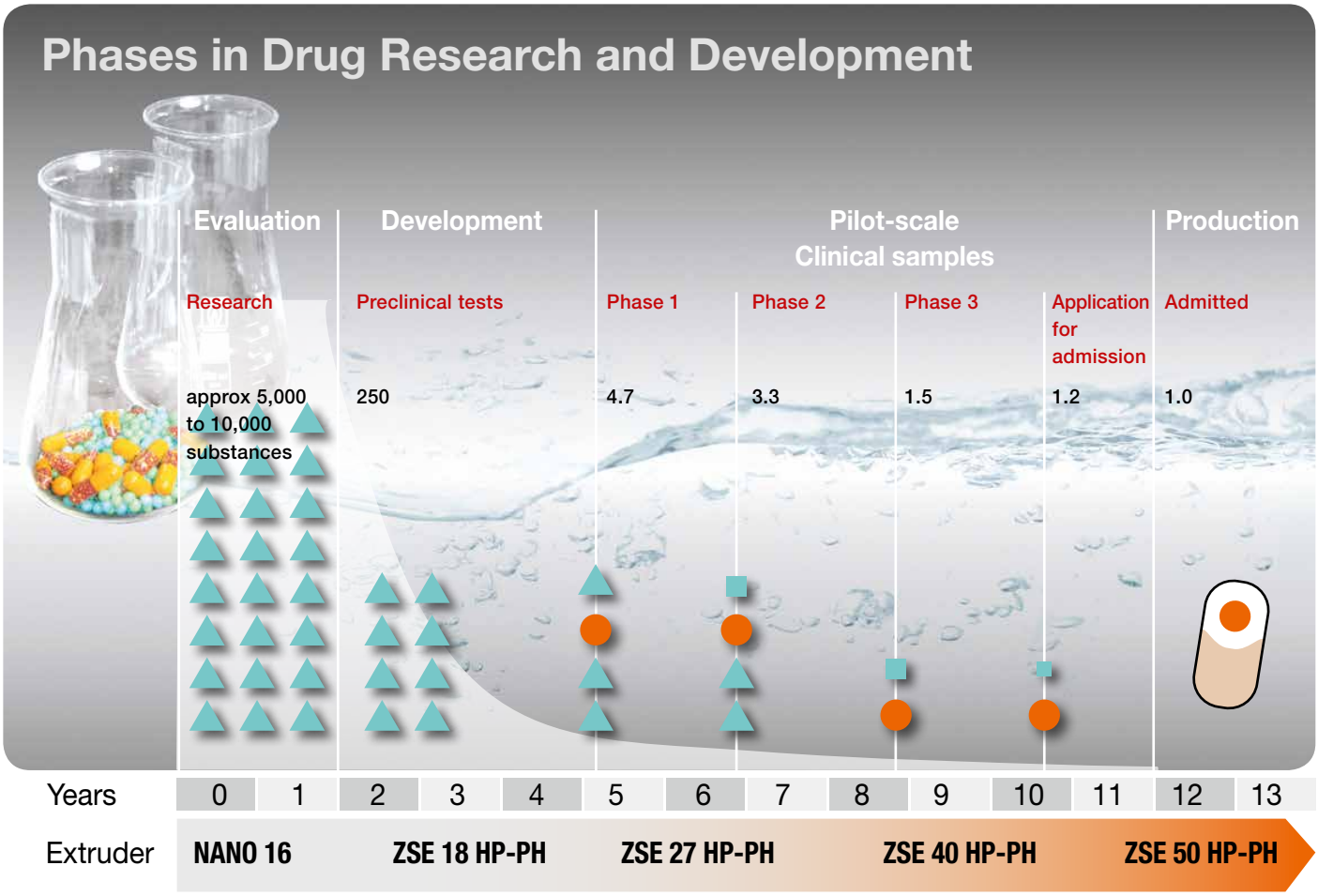
Barrel

The barrels of Leistritz extruders are designed as modular systems, which comprise several barrel modules that are either flanged together or - depending on the size of the line - connected by internal tie rods. There are no sealing elements between the barrels. The sealing is ensured solely by pretensioning force. The cross section of the barrels of the twin screw extruder is characterized by a barrel opening in shape of a horizontal 8. The inner surface of the barrel can have an especially hardened and honed layer in order to minimize corrosion and mechanic wear.

Screw

The screw is the most important part of the extruder. Its design distinguishes the processes that the extruder can fulfill and therefore the quality and quantity of the extruded material. The spiral flights of the screws are whirled into a cylindrical steel rod. There are two ways to manufacture a screw: You can either prepare a so called compact screw or produce a segmented screw, which has proven to be very practical, especially for twin screw extruders. The screw elements are internally splined and can be slid and fixed on the according counterpart - the splined screw shaft. The advantages of the segmented screws are obvious: The screw profile can be altered at any time.

Already in the mid 1980s Leistritz delivered extruders for the pharmaceutical industry. The extrusion lines for wet and hot melt extrusion are renown all over the world and stand for cutting edge technology.



Leistritz offers the appropriate extrusion line for each phase.

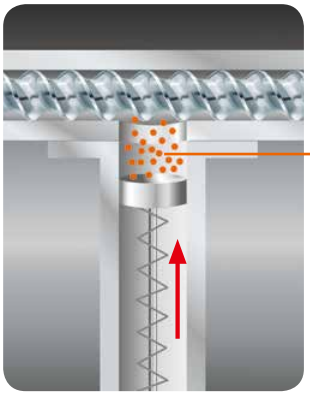
Leistritz pharma extruders at a glance:
GL = co-rotating twin screw extruder

Type	Diam. Screws (mm)	Torque Screws (Nm)	Version	Screw Speed (rpm)	Drive Power (kW)
NANO 16	16	42	GL	500	2.24
ZSE 18 HP-PH	18	71	GL	500 & 1,200	3.9
ZSE 27 HP-PH	27	268	GL	500 & 1,200	15
ZSE 40 HP-PH	40	830	GL	400	37
ZSE 50 HP-PH	50	1,570	GL	400	70

The NANO 16 twin screw extruder, integrated with a new micro-plunger feeder, is used in the evaluation stage, so the extrudability of the formulation is tested (this is no basis for scale-up calculations). By means of its 3-lobed screw elements, it facilitates facilitates the continuous extrusion process for batch samples from 20 to 100 grams. The NANO 16 utilizes a segmented design for barrels and screws, a stainless steel process section, and as an option a state-of-the-art control/data acquisition.

The NANO 16 is mainly characterized by the micro-plunger feeder. Until now, there was no possibility to run very small batches on a twin screw extruder in a starved fed mode. The micro-plunger feeder consists of a piston which slides within a stainless steel tube. The tube is filled with a 20 to 100 cc batch. After being positioned to the bottom of the feed barrel, the piston is pushed upwards by a variable speed drive to facilitate precision feeding at extremely low rates.

The NANO 16 has a torque of 42 Nm, which facilitates processing of highly viscous ingredients.

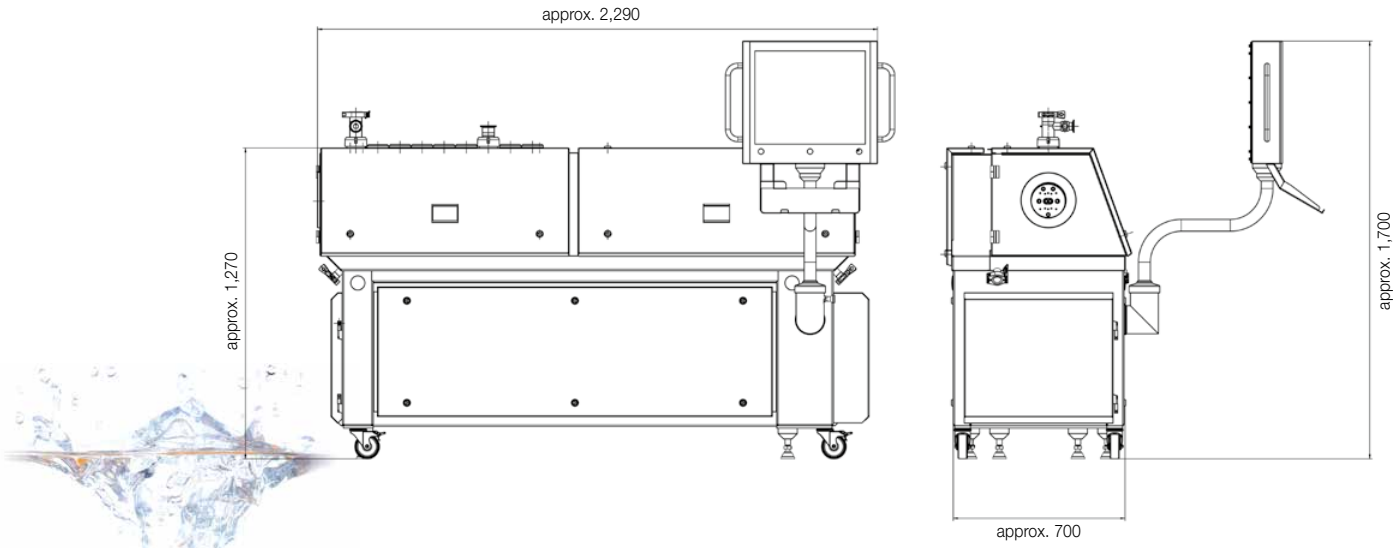


micro-plunger feeder

The NANO 16 is also available as a version with a 12 L/D processing unit and an even smaller micro-plunder feeder. This way small batches of up to 10 cc can be processed.

ZSE 18 HP-PH

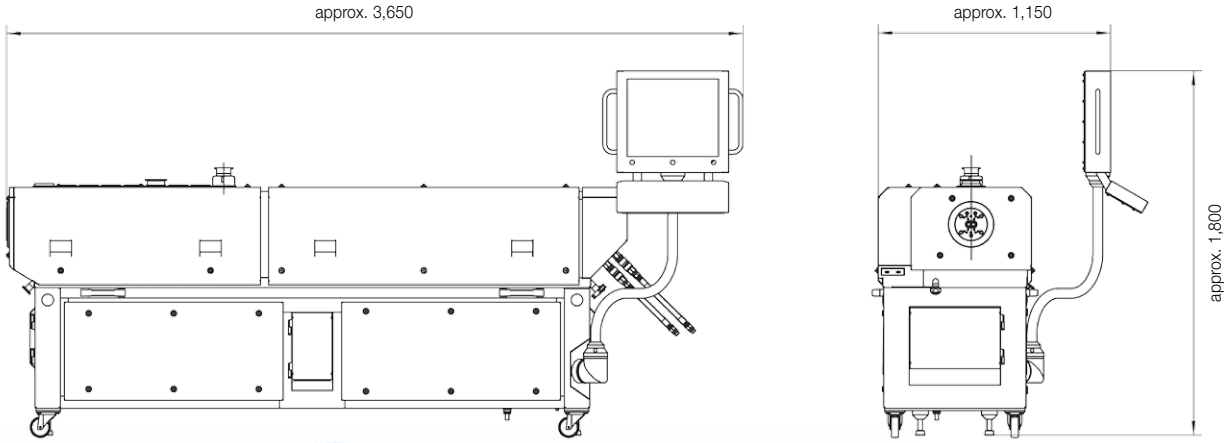
The twin screw extruder ZSE 18 HP-PH is developed for use in labs and small production. It is suited for throughputs from 200 g/h to 5 kg/h.

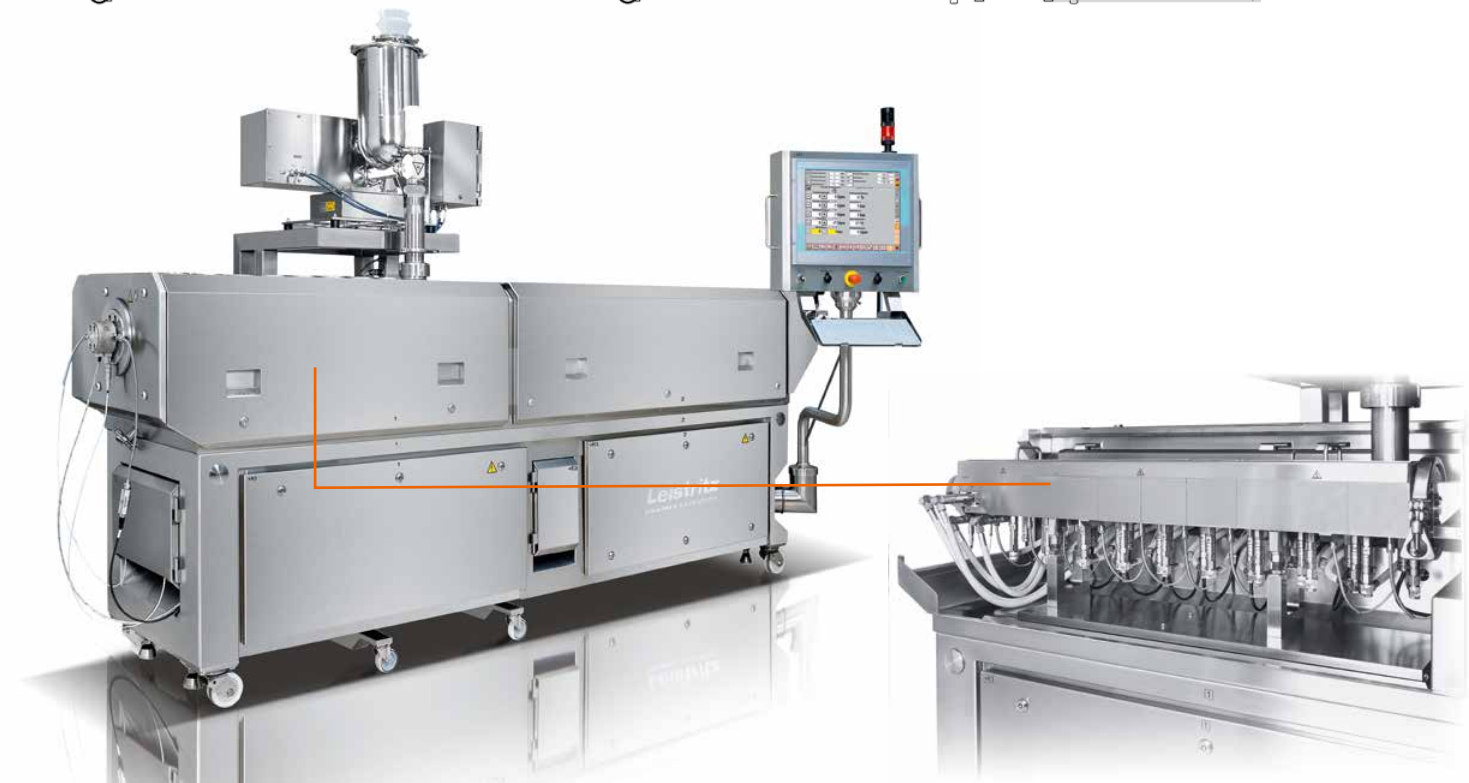


example: ZSE 18 HP-PH

The ZSE 27 HP-PH has all the specific parameters of a large scale production machine in order to be able to project lab scale compounding for production settings as accurately as possible (1 to 25 kg/h).

The processing unit and the drive unit are built as compartments with a subdiving wall - an important feature with regard to the cleaning aspect. The processing unit can be separated from the extruder by means of a trolley. The barrel segments can then be disassembled for cleaning (also see on page 14-15).



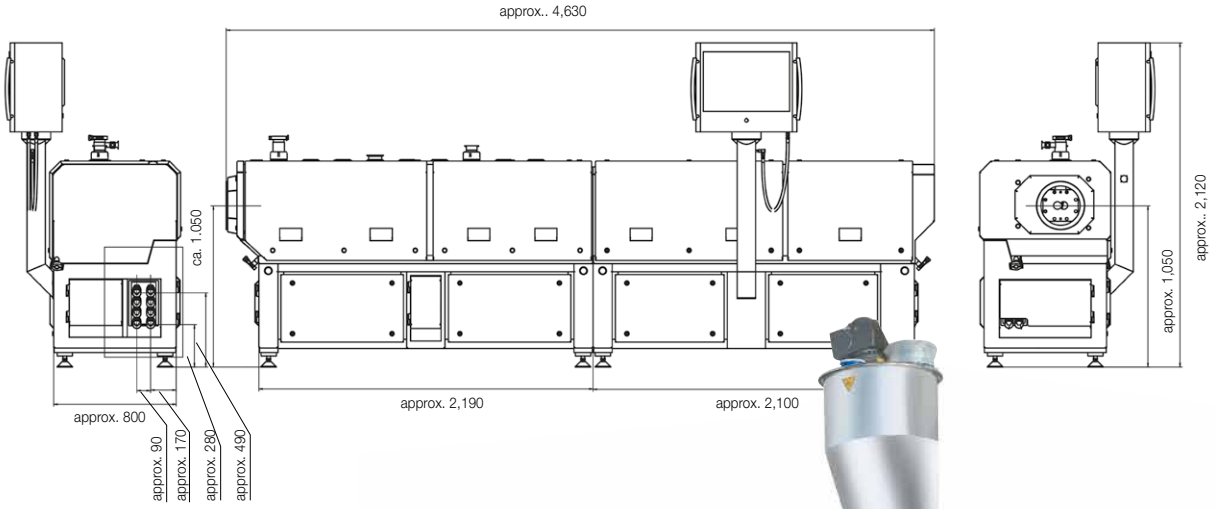


example:
ZSE 27 HP-PH

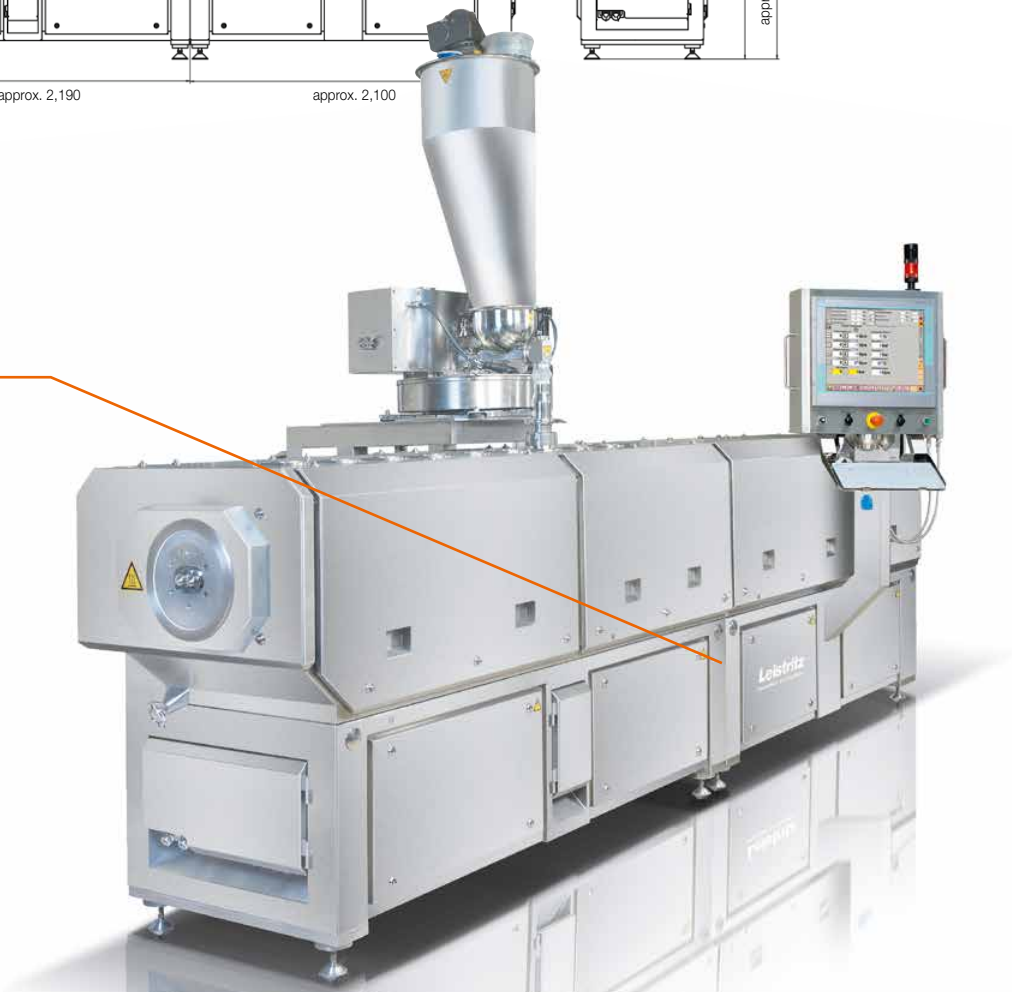
The ZSE 40 HP-PH is designed as a production scale machine.

The frames of processing unit and drive unit are made of stainless steel. The surfaces are polished in order to assure easy cleaning. The cover can be removed manually at any time. This way, necessary reconfiguration of the barrel segments can be done.

The ZSE 50 HP-PH is a production scale machine that is able to gain higher throughputs. Since it is designed with a modular layout, it is adaptable to various processing tasks. The processing unit can be disassembled, cleaned and reassembled with small technical effort.



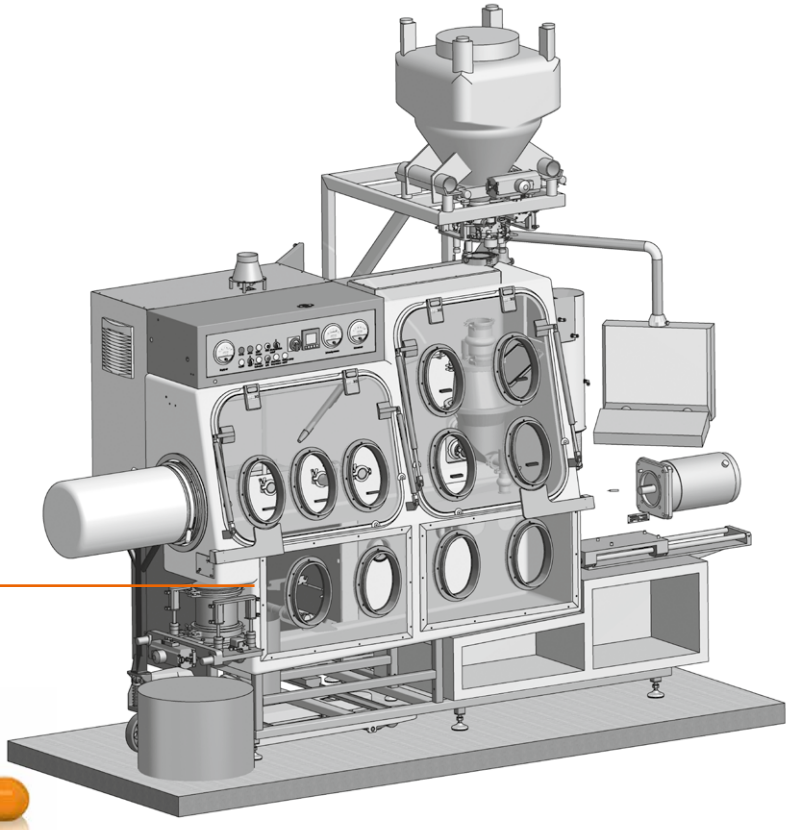
Frames of processing and drive unit are separated. Thus, the two parts can easily be set up even in narrow spaces.



Cleaning of barrel segments:

- detach the pluggable electricity and cooling water supplies
- open the clamping flange and pulling out the barrel
- dock the trolley to the processing unit
- slightly lift of the processing unit and move the trolley aside

Containment:
The significance of processing high potent drugs has grown in Hot Melt Extrusion. This development leads to higher requirements for work safety. The most effective method when working with products of OEL classes 4 and 5 is the isolator technology. The engineering of such a line is a highly demanding task, since three line components have to be isolated: dosing unit, extruder and downstream equipment. The Leistritz engineers have developed customized solutions which meet the requirements in terms of handling in the isolator, cleanliness and hermeticity. A mock-up study ensures the safe and ergonomic work of the operators.

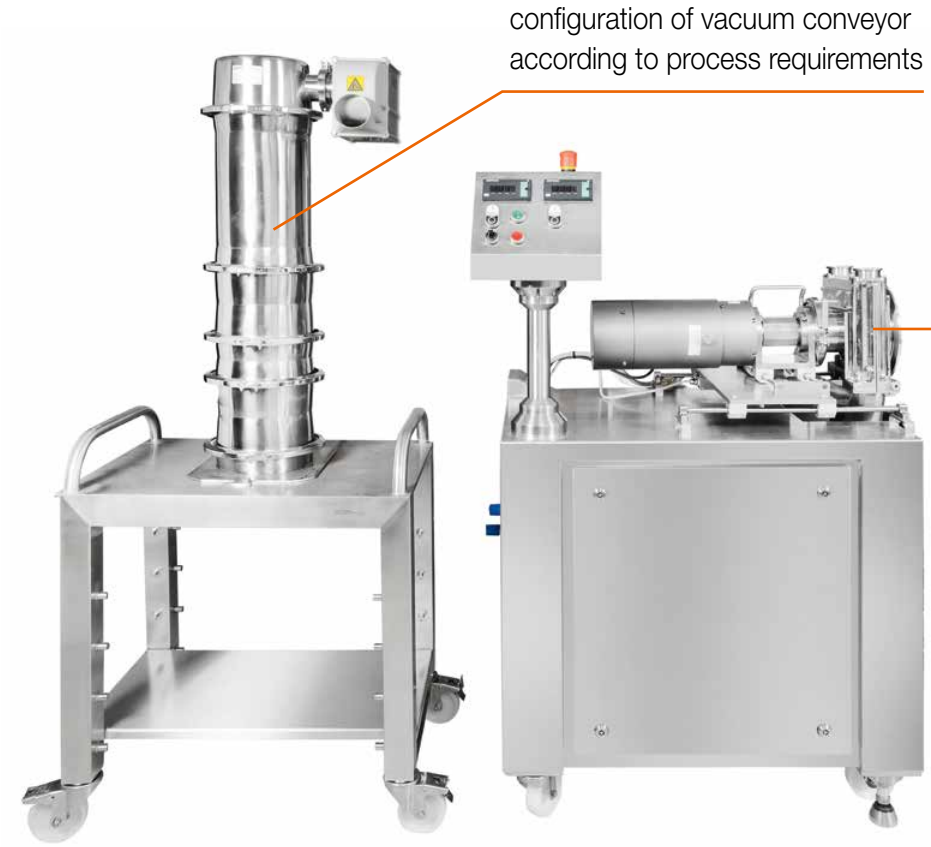


Washing-in-Place:
The washing-in-place-kit simplifies the cleaning. The cleaning tube is plugged to the adapter (notch). The screws and the barrel (made of stainless steel) are rinsed with water. They are disassembled and cleaned in a washing machine.

LMP 2.0

One of the most frequently used pharmaceutical forms for sustained release applications are capsules filled with micro pellets in spherical, semi-spherical and lenticular shapes (approx. 1.5 - 3 mm). The pellet size depends on the formulation and the process parameters.

In combination with Leistritz pharmaceutical extruders, the redesigned LMP 2.0 produces micro pellets in a continuous process. The pellets are cooled off and transported in a circulated air stream. The handling of this device is very convenient. For an effective pressure build up as well as a better melt distribution at the die, a melt pump can be easily integrated. More homogeneous pellets are the result. The LMP 2.0 can be run with or without melt pump. The LMP 2.0 is available in two versions: for the extruder sizes ZSE 18 HP-PH and ZSE 27 HP-PH.



LMP principle:
One or two cutting blades cut the discharged melt and catapult it into the cutting chamber.

Technical Data:

Drive	water-cooled AC drive
Drive power	1.1 KW
Cutting blades	1 - 2, flexible, stainless steel
Blade speed	0 - 3,000 rpm
Diameter of hole circle	50 mm/70 mm
Dimensions (L, W, H)	500 mm x 700 mm x 1,700 mm
	700 mm x 1,250 mm x 1,400 mm
Extrusion height	1,050 mm

Data for LMP 18 2.0

Documentation, Validation and Automation

Documentation and Validation

The validation of pharma extrusion lines within the scope of GMP requirements is inevitable in order to produce constantly high-class products. With its qualification package, Leistritz offers design, installation and operational specifications for the GMP compliant extrusion lines including equipment and computer system (PLC SCADA and visualisation). The package also contains conclusive quality control plans for FATs (Factory Acceptance Tests) and SATs (Site Acceptance Tests).

The great advantage: This qualification package simplifies and reduces the validation effort (for the customer) by referring to test results made by Leistritz during IQ (Installation Qualification) and OQ (Operation Qualification).

Automation

The main objective of Leistritz' automation and control engineering is to integrate all common up- and downstream aggregates necessary in pharma extrusion, in one visualization and operating unit (control of e.g. gravimetric feeder, the start up of pelletizers or liquid feeders). All quality relevant parameters are displayed and recorded.

Consequently, the control unit plays a major role, because it reflects the process. Therefore, it is important to specify the design and verify it in a very early project stage.

With a control unit, which meets the high standards of GAMP and 21 CFR Part 11, Leistritz offers a specifically developed solution for the operation of extruder lines.

Macromatex S7 Pharma:
The main page shows an overview of the whole extrusion line as well as the most important parameters.

Macromatex S7 Pharma

S7 control unit as Human-Machine-Interface (HMI)

based on Microsoft Windows 7, iFix with iHistorian (GE Fanuc or Intellution) and Microsoft SQL data base (MSDE)

Scope of function:

- Operating and monitoring
- Trend graphs with free configuration of groups
- Recipe management
- Start-up assistance (sequence)
- Audit trail
- Batch report function
- Windows security und password administration
- 21CFR11 and 4-eyes-principle as an option possible

Software documentation:

- Hardware design specification
- Software design specification
- Alarm list
- Interlock matrix
- SPS assignment
- MSR list with measuring range and entry limits
- Disaster recovery manual
- Operating manual

Basic Control

Standard control unit

- IP 52 system of protection
- Mounted on the machine frame (left in direction of extrusion)
- Operation and display devices:
  - PPID temperature controllers (amount according to processing length)
  - On- / off-drive
  - Screw speed - potentiometer with default setting
  - Display of screw speed - digital
  - Power consumption (torque) in % - digital
  - Emergency switch off

Further operation and display devices can be integrated in the control unit and/or control cabinet.

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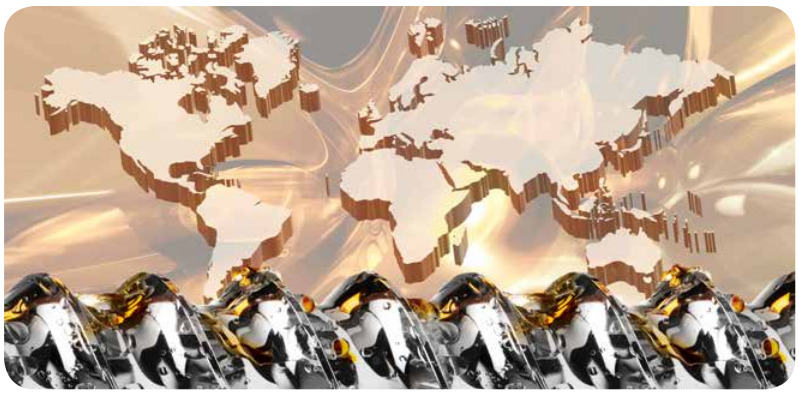

LEISTRITZ EXTRUSIONSTECHNIK GMBH
Markgrafenstr. 29-39 · D-90459 Nürnberg
Phone +49 (0) 911 / 43 06 - 240
Fax +49 (0) 911 / 43 06 - 400
eMail extruder@leistritz.de

LEISTRITZ Machinery (Taicang) Co., Ltd.
Shanghai Branch
Phone +86 21 6352 3268
Fax +86 21 6352 3138
eMail sales@leistritz-china.cn

Leistritz Advanced
Technologies Corp. · BU Extrusion
Phone +1 908 685 2333
Fax +1 908 685 0247
eMail sales@alec-usa.com

LEISTRITZ France Extrusion
Phone +33 (474) 250 893
Fax +33 (474) 250 864
eMail extruderfr@leistritz.com

LEISTRITZ Italia Estrusione
Phone +39 0331 500 956
Fax +39 0331 482 586
eMail info@leistritz-italia.com

LEISTRITZ SEA Pte Ltd.
Singapore office
Phone +65 6569 3395
Fax +65 6569 3396
eMail extruderasia@leistritz.com

refreshing extrusion technology

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