

PHARMACEUTICAL EXTRUSION

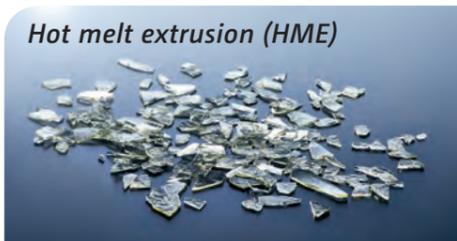
Continuous extrusion process for pharmaceutical masses



PHARMACEUTICAL TWIN SCREW EXTRUSION

Application fields

Compounding with co-rotating twin-screws has been successfully applied in the plastics industry for decades. Now, it is a proven system for hot melt extrusion, granulation, lipid extrusion, transdermals and implants. Leistritz was a pioneer when pharmaceutical extrusion started. Today, we are a technology leader in this area. We have extensive knowledge in the areas of process technology, GMP design, plant engineering, and qualification.



Example after chill Roll process



Solid lipid extrusion

Example of a ZSE 18 HP-PH



Extrusion for transdermal applications



Granulation
Wet extrusion
Wet granulation
Melt granulation

Hot melt extrusion

Hot melt extrusion (HME) is the process of embedding an active pharmaceutical ingredient (API) in a polymeric carrier. Common carrier polymers in the pharmaceutical field are PVP, methylacrylates or cellulose-based carrier materials. During HME the mixture of API, polymer and further excipients is processed at elevated temperature and pressure. The Leistritz ZSE HP-PH blends all ingredients while also imparting high shear to disperse the drug in the carrier at a molecular level, and then forms a solid solution. The extrudate is solidified by being cooled after the discharge at the extruder die. Furthermore, HME has been shown to molecularly disperse poorly soluble drugs of class II and IV in a polymer carrier, increasing dissolution rates and bioavailability.

Solid lipid extrusion

In solid lipid extrusion (also called cold extrusion) lipids are used for the plasticity. As most of the lipids have a low melting point (or range) the extrusion is also a suitable way of processing for thermosensitive APIs. A further advantage is that the process is solvent-free and no solidifying step is needed. Since the lipid forms the matrix it can influence the drug release of the API.

Granulation

Due to their continuous operation twin-screw extruders are very effective in granulation. In wet extrusion and wet granulation finely powdered excipients and APIs are mixed together with a liquid binder in the Leistritz ZSE HP-PH. In **wet extrusion** the mass is discharged through a die as strands, which are pelletized in a subsequent spherulization step. For **wet granulation** no die is applied. Another granulation technique is **melt granulation**. In this process the API containing powders are efficiently agglomerated using a binder which melts during the process and solidifies while cooling. Due to the ability to change the level of mixing within the extruder, a great deal of flexibility in the characteristics of the resulting pellets can be achieved.

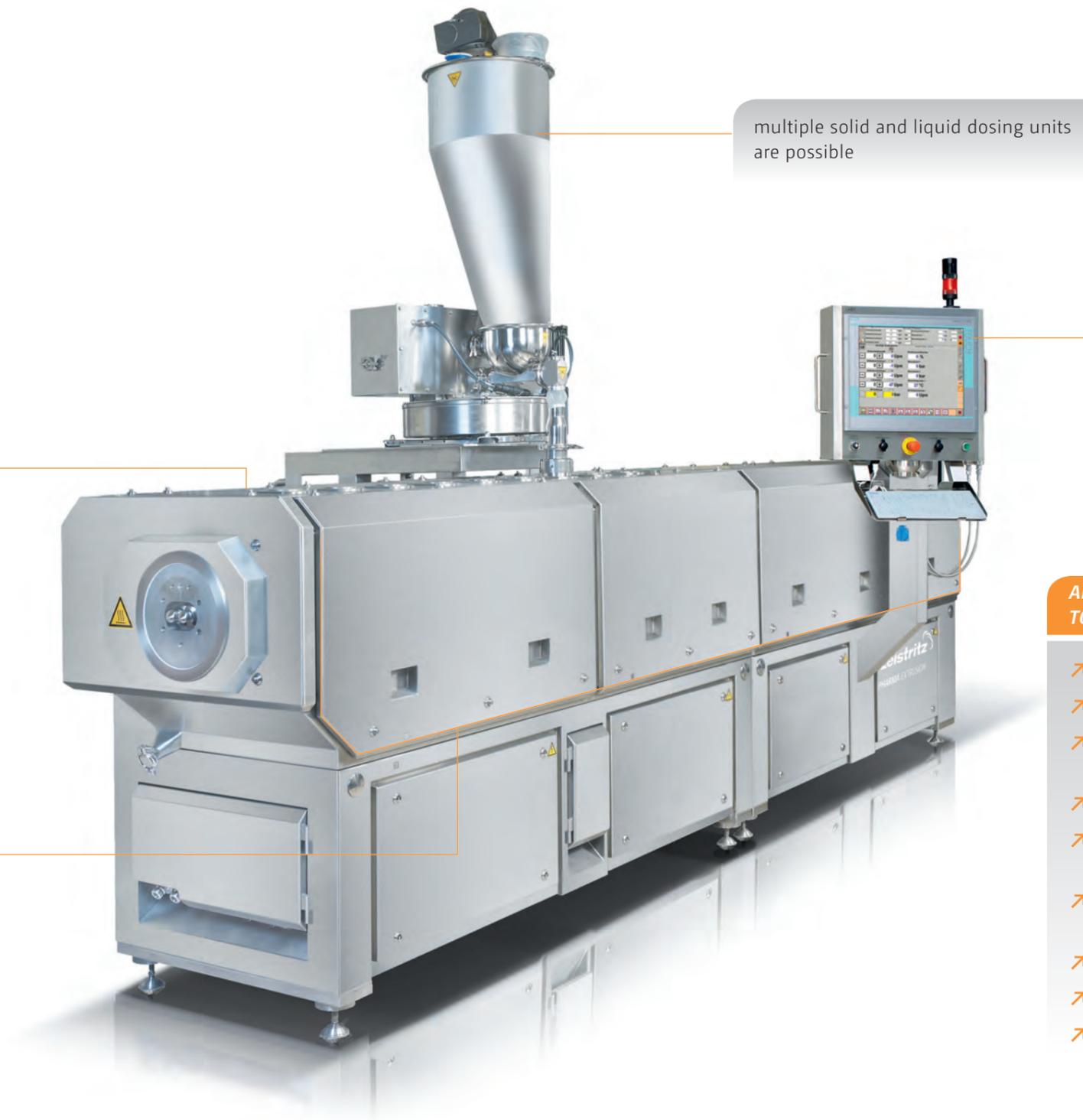
Transdermals

Not only can oral drug formulations, like tablets and pellets, be manufactured by hot melt extrusion, also parenteral depots, for example implants and transdermal patches, can be produced and are state-of-the-art.

TWIN SCREW EXTRUDER **SETUP**

Continuous extrusion process

Extrusion technology is an accepted method for the continuous processing of pharmaceutical materials, and it often offers significant advantages compared to batch processes. In an extruder a number of processing steps are combined, including feeding, melting, mixing, venting, and discharge. Upstream materials handling and downstream equipment work in conjunction with the extruder to perform the intended manufacturing operation. Here is an example of a typical twin screw extruder setup:



multiple solid and liquid dosing units are possible

The control unit facilitates online monitoring and accurate adherence of the set process parameters.

closed processing unit to prevent cross contamination

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 for reconfiguration of the barrels, if necessary.

ADVANTAGES OF TWIN SCREW EXTRUSION COMPARED TO CONVENTIONAL MANUFACTURING TECHNIQUES:

- integration of several process steps in one machine
- small footprint, even for high throughput rates
- excellent mixing capabilities (distributive and dispersive)
- short processing time
- scale-up of results from R&D to production machines
- adjustment of process conditions via flexible screw geometry and other process parameters
- reproducibility of process parameters
- quality by design
- PAT technology

» We are passionate about what we do. That is what brought us to be the leading extrusion line manufacturer in pharmaceutical applications. «

PROCESS KNOW-HOW

Understanding the heart of the extruder

The processing unit is the heart of the extruder. The modular barrel and screw design allows for maximum flexibility. They are specifically designed for the formulation being processed.

Processing length

The processing length (numbers of barrels used) in general depends on the processing task. A typical length for HME is for example 40D. However, some wet granulation or wet extrusion processes only require 20D.

Barrel temperature

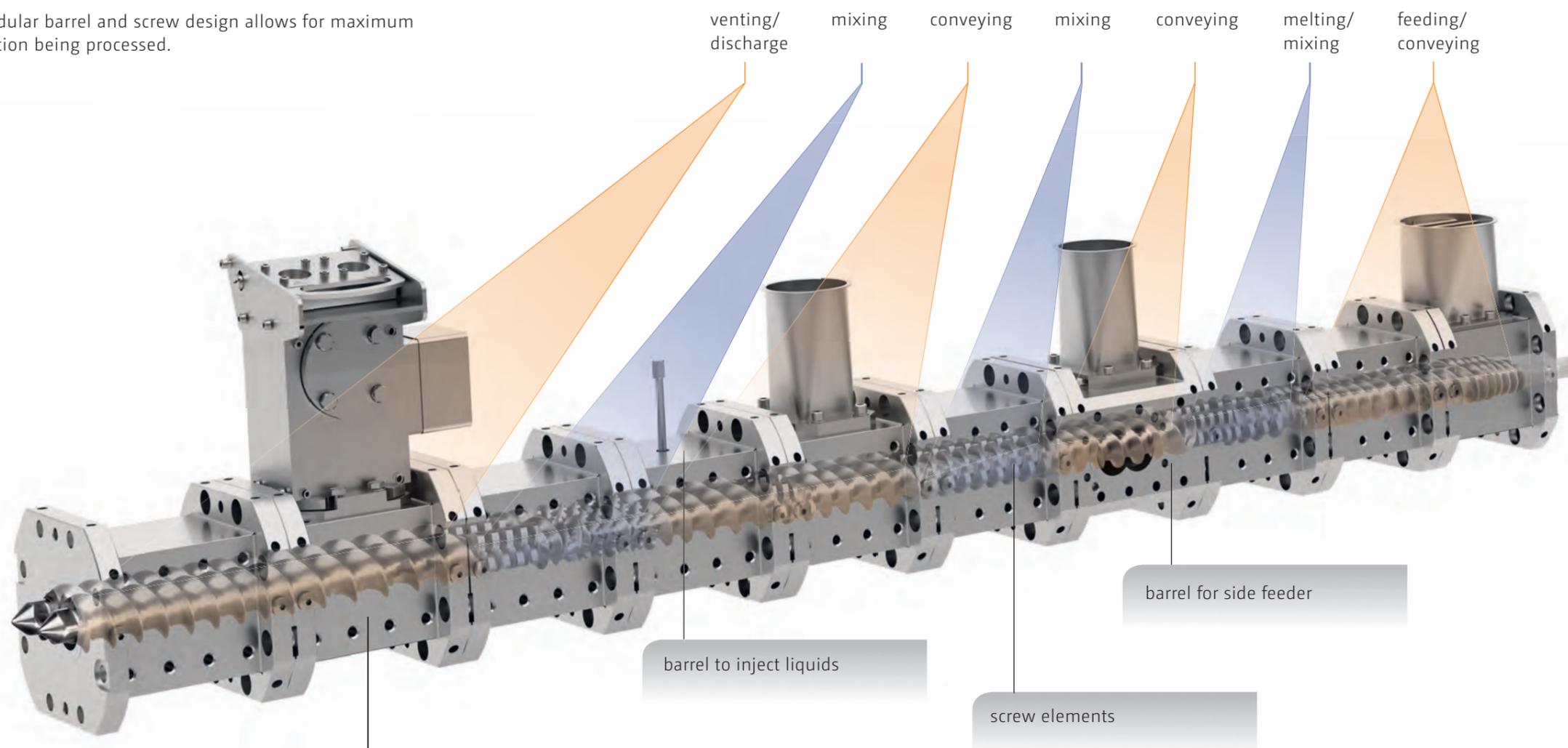
The first barrel is permanently cooled to avoid blockages of the material feed caused by stickiness. Subsequent barrels are both electrically heated and water cooled to maintain a defined temperature. They can support plastification of the material, or can cool down the melt to a desired temperature value.

Vent/vacuum

An atmospheric vent or vacuum removes volatiles or water. To maximize the degassing capability the renewal of the surface has to be maximized. This can be done within different process parameters like screw pitch, filling level and screw speed.

Injection nozzle

Injection nozzles allow the closed addition of liquid components via various pump systems. These range from water or solutions like PVP as binders in wet extrusion/granulation, through to addition of plasticizers or flavours in HME.



Side feeding

A twin screw side feeder facilitates the feeding of powder into the processing unit of the extruder. A thermally sensitive API can be added to the process after the plastification zone to reduce residence time and its exposure to shear stress. This can often be seen with regard to the stability data.

Screw design

The screw design will mainly influence the process, as well as, the product quality and quantity to be processed. Either the screw is made out of one workpiece (so-called compact screw), or it is segmented. Segmented screws will give you more flexibility in the development phase when the process is not fixed yet. The screw elements can be divided, according to their function into conveying elements, mixing and zoning. The competence of the Leistritz processing expert is to create the optimum screw design for the respective application.

LEISTRITZ ZSE HP-PH

Twin screw extruder overview

We have been delivering twin screw extruders for the pharmaceutical industry for more than 30 years. The extrusion lines for wet and hot melt extrusion are renowned all over the world for our cutting edge

technology. Leistritz offers the appropriate line for each phase in drug research and development, as well as for large scale production.

Scale-up

The Leistritz family of extruders covers the need for feasibility testing with very small amounts through to volume production with maximum throughputs and utilization. Our laboratory systems are highly configurable for method development, and the consistent geometry of the ZSE HP-PH series ensures effective scale-up throughout the range. Our processing know-how is available for all stages of the project.

» In the lab or in 24 hour volume production, Leistritz have a machine solution, and the process know-how to ensure effective scale-up. «

LEISTRITZ EXTRUDERS CONVINCED OF THE FOLLOWING ADVANTAGES:

- well-thought out GMP design
- a vast engineering and processing know-how
- 21 CFR PART 11 conform control units
- qualification package



Example of a NANO 16



Example of a ZSE 12 HP-PH



Example of a ZSE 18 HP-PH



Example of a ZSE 27 HP-PH



Example of a ZSE 40 HP-PH



Example of a ZSE 50 HP-PH

type	screw diameter (mm)	torque screws (Nm)	screw speed (rpm)	drive power (kW)	L x W x H (approx. mm)
NANO 16	16	42	500	2.24	1,200 x 800 x 1,100
ZSE 12 HP-PH	12	20	1,000	2,8	1,500 x 800 x 1,200
ZSE 18 HP-PH	18	74	1,200	10	2,290 x 700 x 1,270
ZSE 27 HP-PH	27	267	600	18	3,650 x 1,150 x 1,800
ZSE 40 HP-PH	40	827	600	51	4,000 x 1,400 x 2,100
ZSE 50 HP-PH	50	1,572	500	65	4,630 x 1,800 x 2,120

GMP EXTRUSION LINES

Easy cleaning and high functionality

For the highly demanding standards in the pharmaceutical industry, Leistritz presents an extruder series including according auxiliary equipment in GMP design – specially designed for pharmaceutical applications.

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.



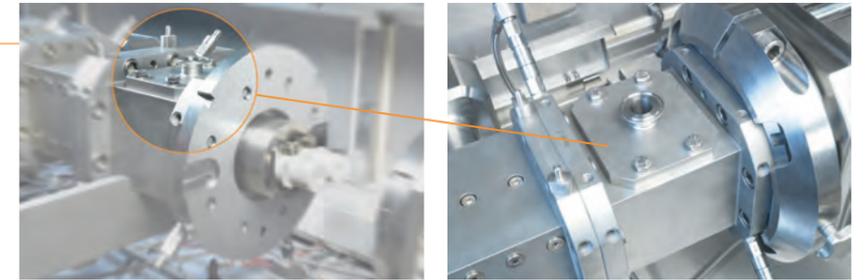
Example of a GMP extrusion line (melt granulation with pellet cooling and transport)

GMP FEATURES

Design highlights

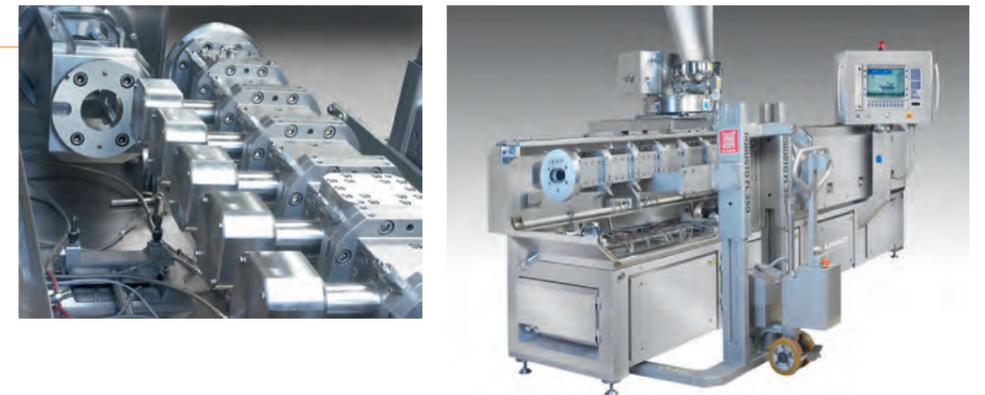
Washing-in-place

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



Barrel handling device

After the processing unit is disconnected, it can easily be removed via the lifting device



Subdividing wall



clamping flange

quick-release coupling

IP 65 heater shells



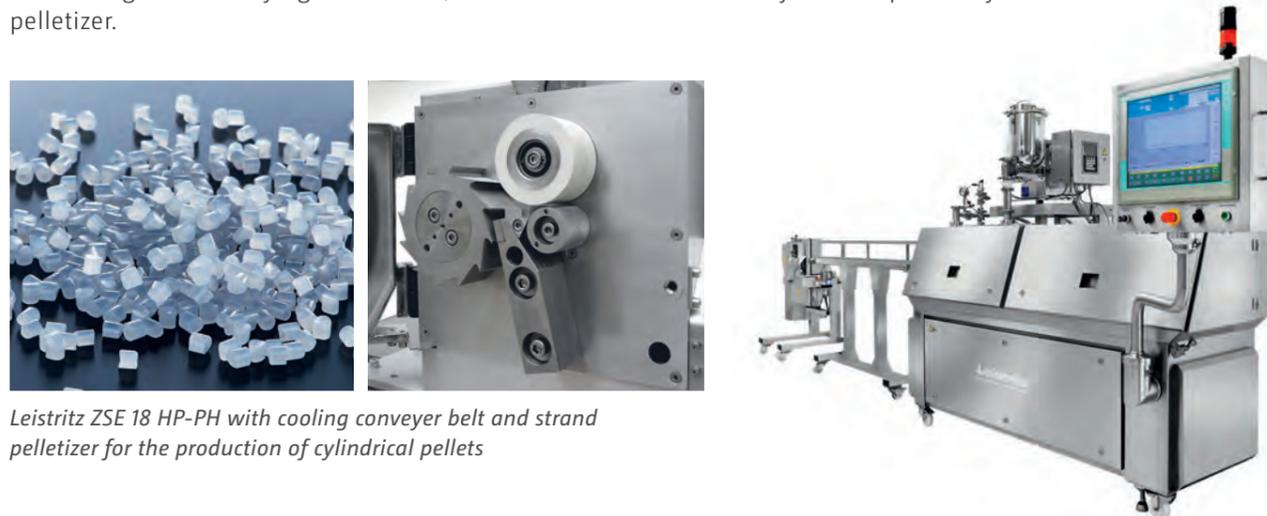
LEISTRITZ EXTRUSION LINES

Engineering know-how

Depending on the formulation and the end product various plant options are available. Here we will introduce the most established ones.

Strand pelletizing

The main step after the extrusion process is the cooling-off phase; therefore, depending on the formulation different options are possible. The most common method is to use a cooling conveyer belt, where the cooling media is air. Efficient horizontal or vertical water cooling baths are available when the process allows water contact. After the cooling and solidifying of the melt, the strands can be cut into cylindrical pellets by means of a strand pelletizer.

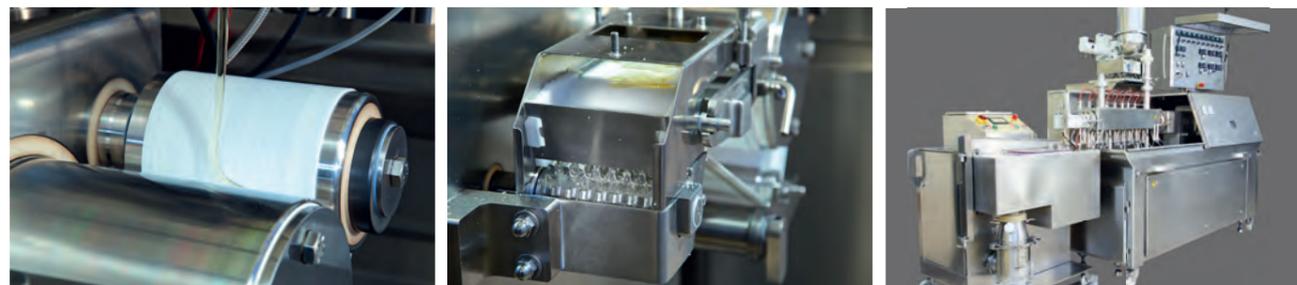


Leistriz ZSE 18 HP-PH with cooling conveyer belt and strand pelletizer for the production of cylindrical pellets

Chill-roll

Another option to cool down the melt is to roll out the melt after discharge onto a chill-roll. With this technique high temperature differences of more than 100°C (depending on the specific heat capacity of the product) can be realized within a short time. The temperature of the chilled roll can be adjusted by a separate chiller. After the quenching, a breaker crushes the solidified melt into smaller pieces. If needed, a subsequent inline milling step can be added. Depending on the desired particle size different mill types are available.

Chill-roll with integrated mill



Micro Pelletizing

Furthermore, it is possible to cut the melt directly in the hot stage. For example with the Leistriz Micro Pelletizer (LMP) 2.0 spherical pellets in the range of 0.5 to 3 mm diameter can be produced. Those pellets can directly be filled into capsules. An option to get a constant material flow and a narrow particle size distribution, is the integration of a gear pump between twin screw extruder and pelletizer. Besides the formulation, dissolution profiles can be adjusted by changing the diameter of the die holes and/or the speed of the cutter knives.

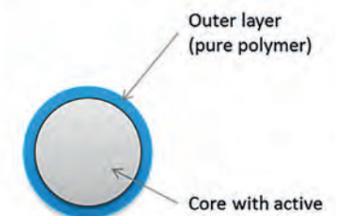


Example of Kollidon SR®-Theophyllin (40%) micro pellets made on a LMP 2.0

Co-extrusion

Co-extrusion implies the simultaneous hot-melt extrusion of two or more materials through the same die, resulting in a multilayered extrudate. Two extruders are used: one for the inner section (mainly containing the API) and one for the outer ring (which in general consists of a drug-free polymer). As the drug release rate from matrix systems is typically governed by drug diffusion through the polymer section, precise control of the inner and outer diameter is crucial.

Example of a multilayered, co-extruded strand



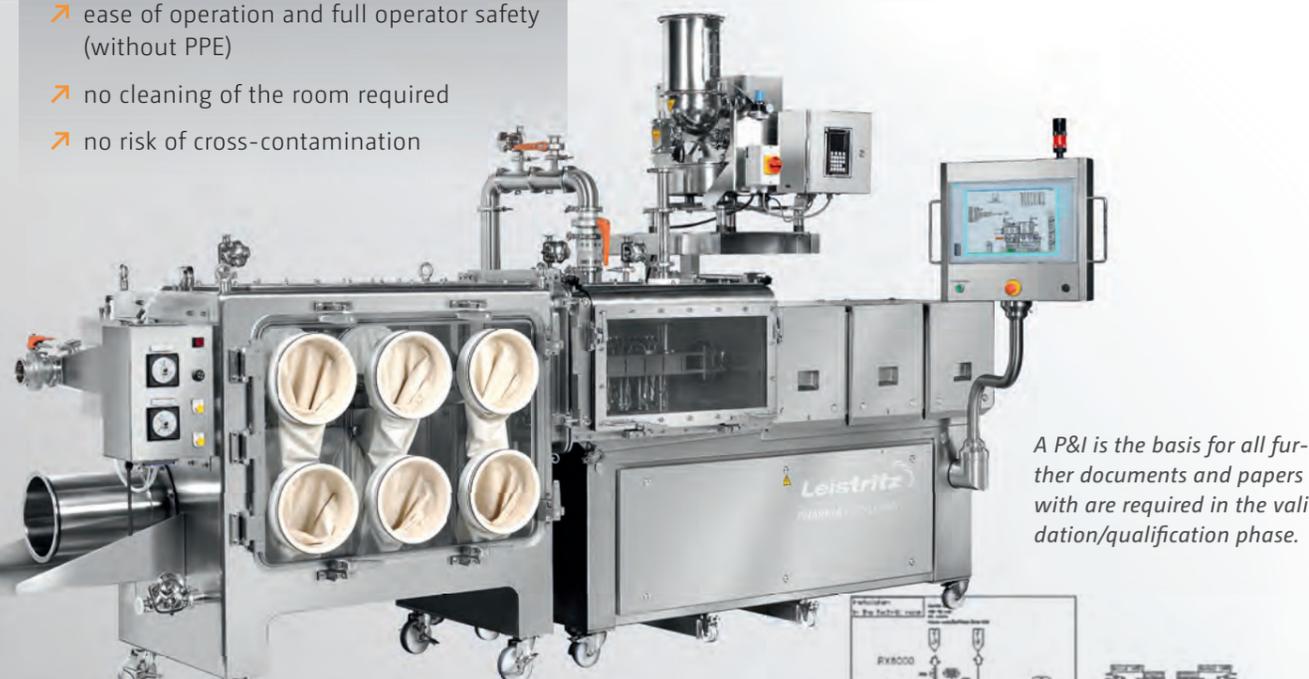
LEISTRITZ CONTAINMENT SOLUTIONS

Engineering know-how

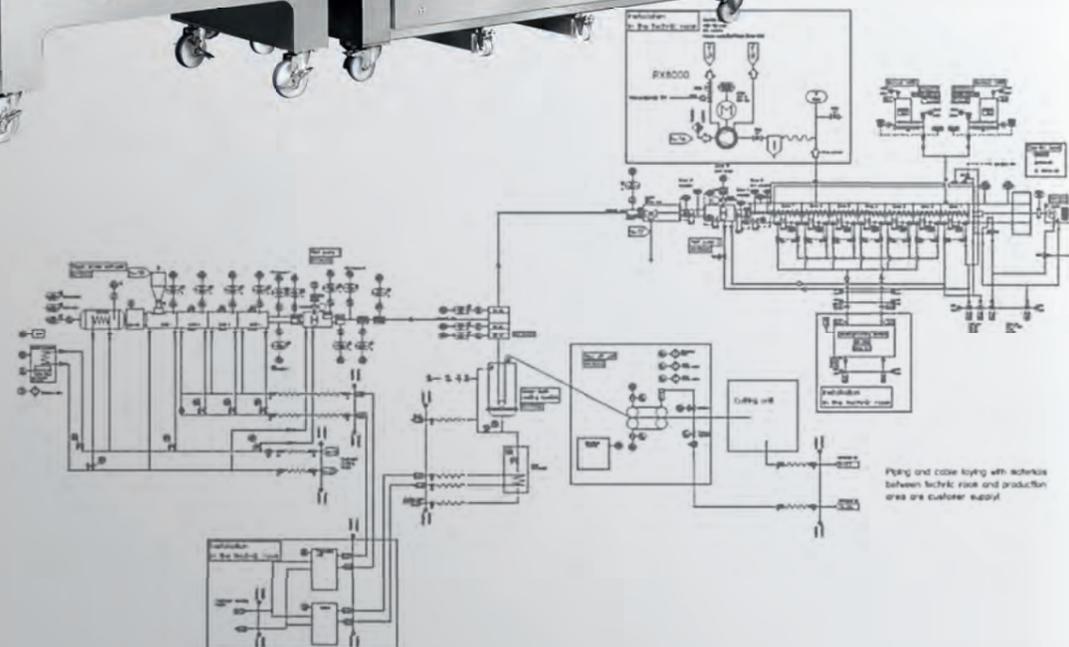
As more and more APIs are classified as highly hazardous substances the operators' safety is a vital issue. This shows the need for new designs of extrusion lines with containment solutions which have already been designed by Leistriz for different kind of OEL levels.

WHY CHOOSE A CONTAINMENT SOLUTION?

- ease of operation and full operator safety (without PPE)
- no cleaning of the room required
- no risk of cross-contamination



A P&I is the basis for all further documents and papers which are required in the validation/qualification phase.



Extrusion line OEL 5 (<math><1\mu\text{g}/\text{m}^3</math>)

ENGINEERING REQUIREMENTS

- At least three line components have to be integrated in the containment system: dosing unit, extruder, downstream equipment.
- handling in the isolator, dismantling of processing unit without tools
- Safe and ergonomic work of the operators have to be ensured.
- WIP process

» To put an extrusion line in an isolator is a complex task and needs a very good understanding of GMP, as well as a solid engineering expertise. «

STATE-OF-THE-ART GxP CONTROL SYSTEM

GxP conform operating and monitoring

When designing a twin screw extrusion plant all aspects specific for pharmaceutical applications must be taken into consideration. An extruder unites a high level of mechanical standard components and functions with various customized adaptations. The main objective of Leistriz' automation and control engineering is to integrate all common up- and downstream aggregates necessary in pharmaceutical extrusion in one operating unit.

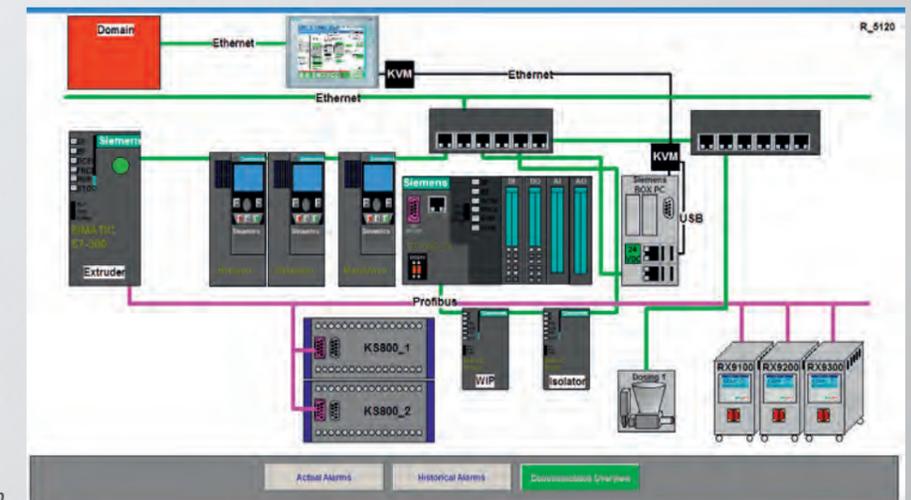
- The hardware and software is based on industrial standards: Siemens TIA control, GE SCADA system iFIX with touch panel.
- The application software satisfies all regulatory rules, such as 21 CFR part 11.
- Leistriz control units are stand-alone solutions, either just for the extruder or for the integration of a complete plant.
- The integration with existing ERP or MES systems and central data storage is possible.
- Centralized password and security solutions can be connected to production and IT networks.



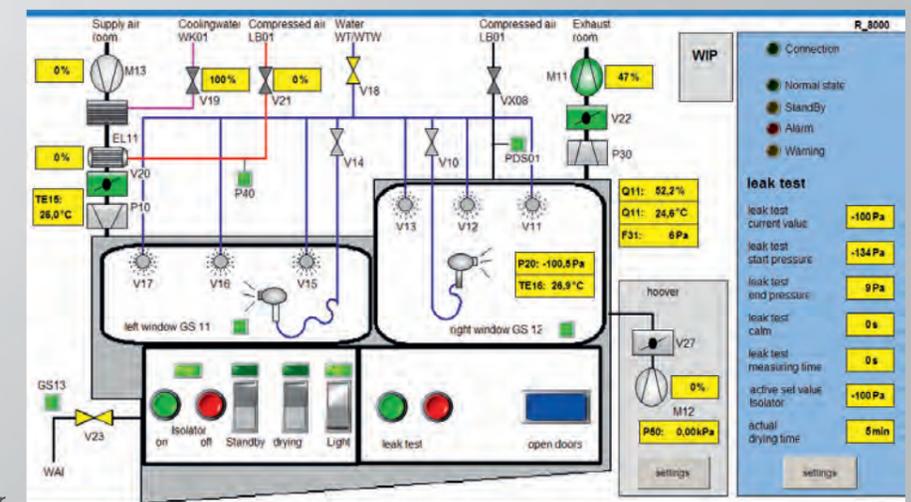
With the Leistriz software you can focus on your processes. From controlling a stand-alone extruder to the integration of all components of a whole extrusion line you will need only one software, which grows with its requirements.

THE LEISTRIZ CONTROL UNIT COORDINATES ALL PROCESSES:

- start-up and shut down
- formulation management
- batch management
- cleaning
- data storage



Example of the line setup



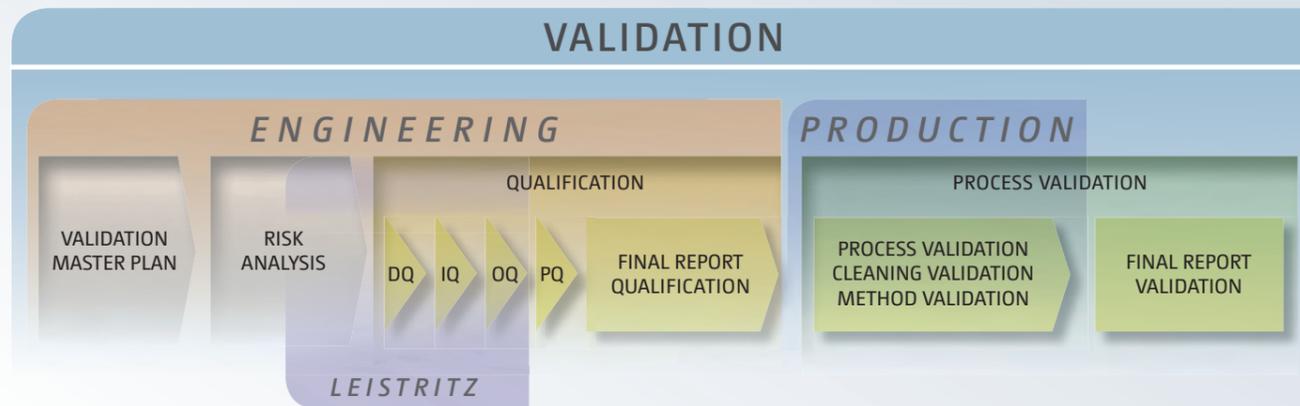
Visualization example of the isolator

VALIDATION & QUALIFICATION

Consideration of highest quality standards

The validation of pharma extrusion lines is inevitable in order to constantly produce high-class products. The Leistritz qualification package includes, depending on the specific project, design qualification (DQ), installation qualification (IQ), and operational qualification (OQ). IQ and OQ are typically performed during

the factory acceptance test (FAT) and the site acceptance test (SAT). 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 and OQ.



Overview: engineering and production phase

TYPICAL MILESTONES AND TESTS	
user requirements specification (URS)	user
validation master plan	user
quality & project plan	Leistritz
functional design specification (FDS)	Leistritz
➤ hardware design specification (HDS)	
➤ software design specification (SDS)	
➤ interface specification	
realization	Leistritz
traceability matrix on demand	Leistritz
factory acceptance test (FAT) incl. IQ/OQ tests	Leistritz
site acceptance test (SAT) incl. IQ/OQ tests	Leistritz
performance qualification (PQ)	user

» Leistritz supplies a state-of-the-art documentation package for the full extrusion line. «



TESTING & OPTIMIZING
Leistritz extruders in use worldwide

Global cooperation with institutes, universities and development partners is an important part of the Leistritz philosophy. Through our research and development projects, we are working on the future and expanding our process engineering and machine know-how.

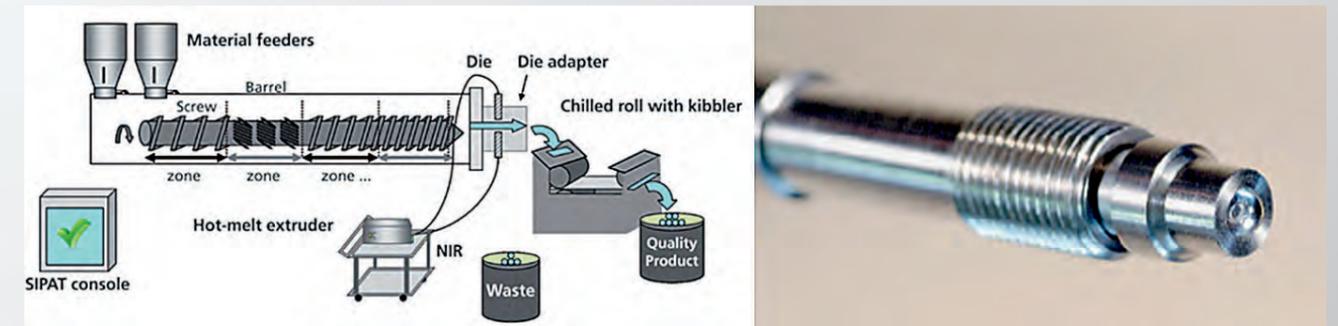
With laboratories in Nuremberg (Germany) and Somerville (USA), we provide an environment capable of helping our customers to put their products to the test. Processes are tested, evaluated and optimized

here on our lab extruders and equipment. Not only does Leistritz offer its customers two laboratories for feasibility studies, but in cooperation with partners, we also provide a fully equipped development and upscaling center. There our customers can develop, test and produce solid pharmaceutical forms with up-to-date manufacturing technologies in a GMP and FDA compliant surrounding. In the lab of our cooperation partner, Leistritz customers can work on a ZSE 18 HP-PH extruder amongst other ancillaries with analytical support available.

Process Analytical Technology (PAT)

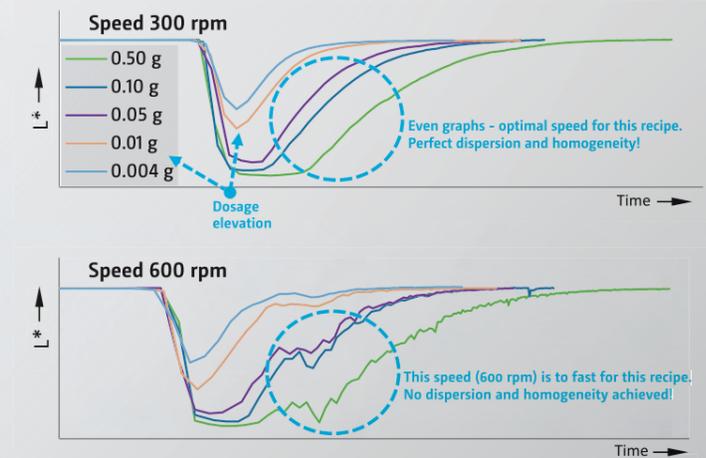
A continuous manufacturing method as extrusion is ideal for a quality by design approach. Based on a risk analysis the critical quality attributes can be defined and continuously monitored. In addition to the typical extrusion process parameters like melt temperature, melt pressure, and specific energy consumption, inline monitoring can be applied.

Common technologies are Raman and NIR. Leistritz also provides the possibility to use In-line technologies like UV-Vis measurement. This new method immediately gives you the chance to evaluate the impact of screw configuration as well as screw speed on product homogeneity and stability, residence time distribution and thermal degradation. Furthermore feeding accuracy can easily be monitored.



Example: Determination of optimum screw speed and elevation in dosage system

Five concentrates with identical base material were processed with two different speed levels.



INLINE PROCESSING MONITORING ALLOWS TO

- identify optimum screw speed.
- determine optimum dispersion and homogeneity.
- detect dosage elevations.
- identify off-spec batches, waste and contamination.

OUR EQUIPMENT IN THE LEISTRITZ LABS

- NANO 16
- ZSE 12 HP-PH
- ZSE 18 HP-PH
- ZSE 27 HP-PH
- Leistritz Micro Pelletizer
- sugar pelletizer
- cooling conveyer belt
- strand cutter
- chill-roll (upon request)
- PAT

» We accompany our customers throughout the whole development phase: We conduct tests, produce clinical batches in cooperation with institutes and partners or provide rental machines. «



LEISTRITZ *TWIN SCREWS*

Now and then

Developed almost 100 years ago for food and natural rubber/plastics applications, twin screw extrusion generates some of the most cutting-edge drug delivery systems available. Processing with twin screws offers significant advantages as compared to batch manufacturing techniques. An advantage is that solvents and water are generally not necessary for processing, which reduces the number of processing steps because expensive drying equipment and time consuming drying steps can be omitted.

Interest in extrusion by the pharmaceutical industry began in the 1980's. Leistritz was a pioneer in the pharmaceutical world and one of the first extruder manufacturers to develop twin screws for this application field. In the meantime technology has improved immensely.

The move towards efficient continuous processes like extrusion in pharmaceuticals mirrors the events of some 80 years ago in the plastics and food sectors. Also the ability to mix materials to customize product performance caused visionary pharmaceutical scientists to consider extrusion to enable therapies of poorly soluble compounds through the generation of amorphous solid dispersions. The recognition of melt extrusion has led to further research efforts and understanding of how the technology can be applied and resulted in traditional plastics process techniques being transferred to manufacture novel dosage forms and unique multifunctional medical devices.

Leistritz twin screw extrusion lines are among the leading machines in the pharmaceutical market worldwide. They must satisfy the highest production and quality requirements every day. Our formula is to work in an efficient and economical manner. Our technical support has a proven track record with extruders and extrusion lines and it is active around the world for you. Competent and solution-oriented professionals make sure that your technology always stays operational.

OUR SERVICE OFFERS:

- assembling/commissioning
- revamping
- original spare parts
- trials in our pharmaceutical labs in Germany and USA
- consultation in the field of process engineering
- training sessions, also specifically developed inhouse training
- rental equipment partners for contract manufacturing
- cooperation with universities and institutes
- Leistritz Service Hotline: **+49 911 / 4306-444**

» *Our team is on the road for our customers all over the world, with a high amount of expertise and always solution-oriented.* «



1980's



1990's



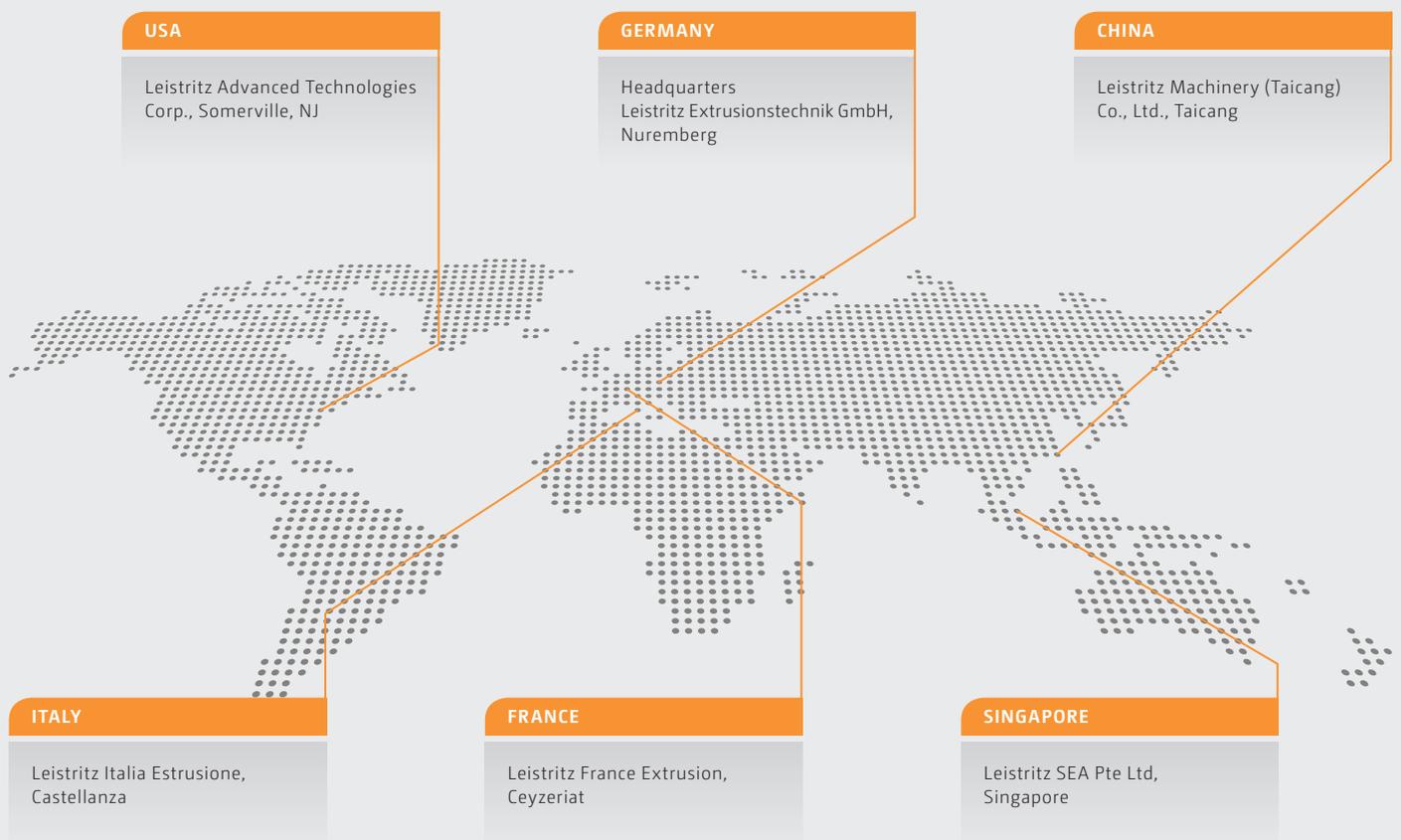
2000



2015

EXTRUSION TECHNOLOGY

Available for you all over the world



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