PHARMACEUTICAL EXTRUSION

Continuous extrusion process for pharmaceutical masses

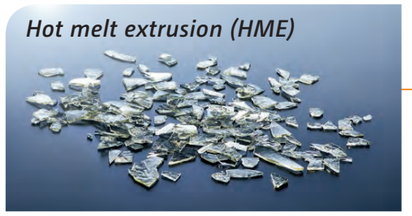
↗ Overview

PHARMACEUTICAL
TWIN SCREW EXTRUSION

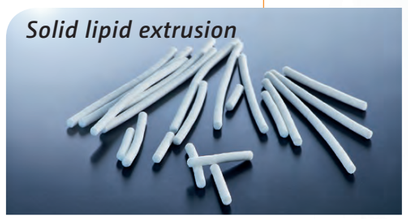
Application fields

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 technology leader in this area. We have extensive knowledge in the areas of process technology, GMP design, plant engineering, and qualification.

Example of a ZSE 18 HP-PH



Example after chill Roll process



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, just to name a few. During HME the 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 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 2 and 4 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 suitable way of processing for thermosensitive API's. 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 API ingredients 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 spheronization step. For **wet granulation** no die is applied. Another granulation technique is the **melt granulation** where API containing powders are efficiently agglomerated by the use of a binder which melts during the process and solidifies after having cooled down. 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 oral drug formulations like tablets and granules can be manufactured by hot melt extrusion, also parenteral depots for example implants and transdermal patches are state-of-the-art.

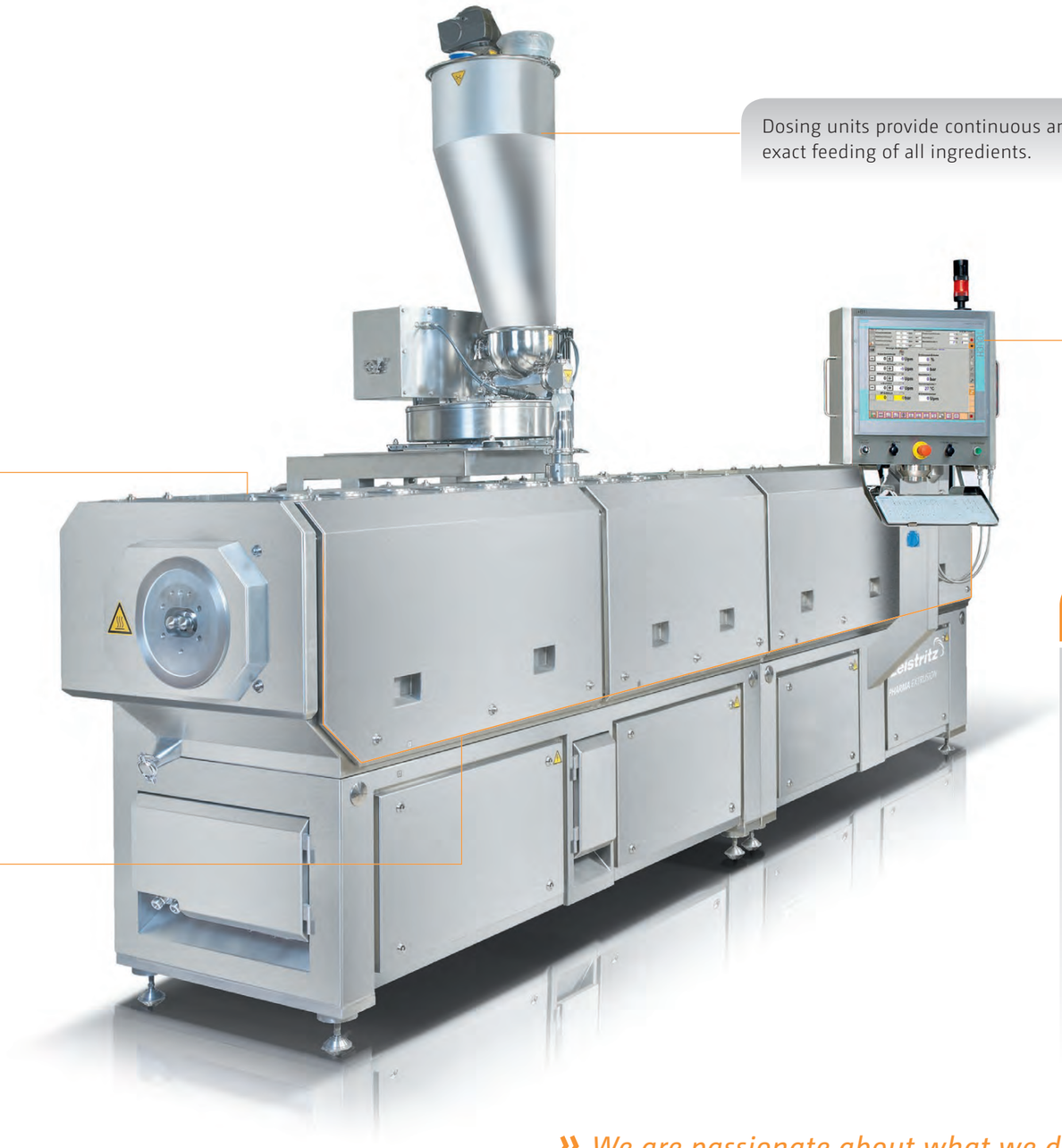
TWIN SCREW EXTRUDER ***SETUP***

Continuous extrusion process

Extrusion technology is an accepted method for the continuous processing of pharmaceutical materials, and often offers significant advantages compared to batch processes. In an extruder a number of processing steps are combined, which include 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:

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 at any time. This facilitates reconfiguration of the barrels, if necessary.



Dosing units provide continuous and exact feeding of all ingredients.

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

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
- reproducability of process parameters
- quality by design
- PAT technology

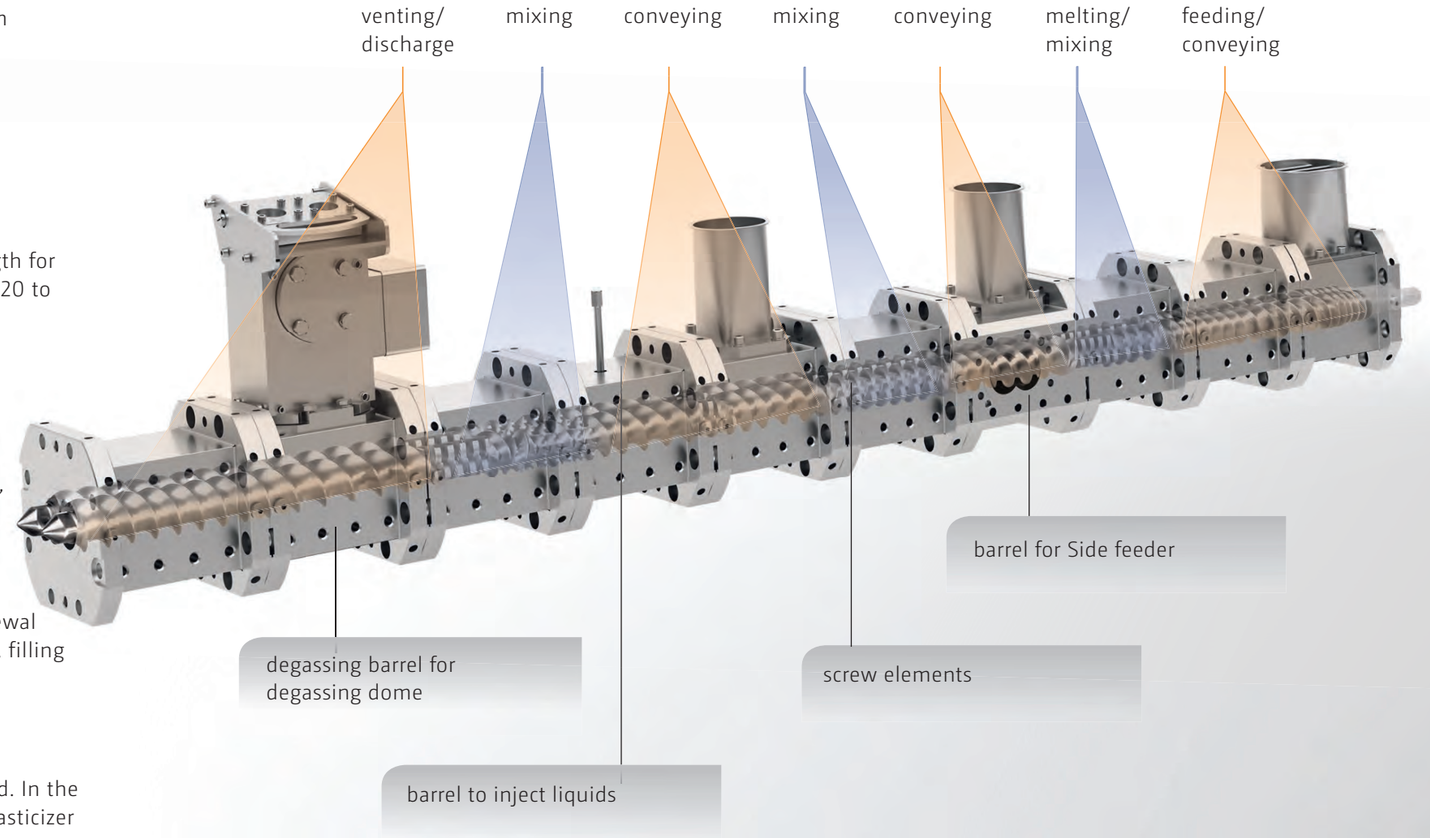
» We are passionate about what we do. That is what brought us to be the leading extrusion line manufacturer in pharmaceutical applications. «

↗ Screws & barrels

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, designed specifically 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, for most of the wet granulation or wet extrusion processes a length of 20 to 30D is sufficient.

Barrel temperature

Except for the first barrel each zone can be electrically heated or water-cooled to a defined temperature. The first zone is permanently cooled to avoid a blockage of the material feed caused by stickiness. The barrel temperatures can have different functions: Either they can support the plastification of the material, or they cool down the melt to a desired temperature value.

Vent/vaccum

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

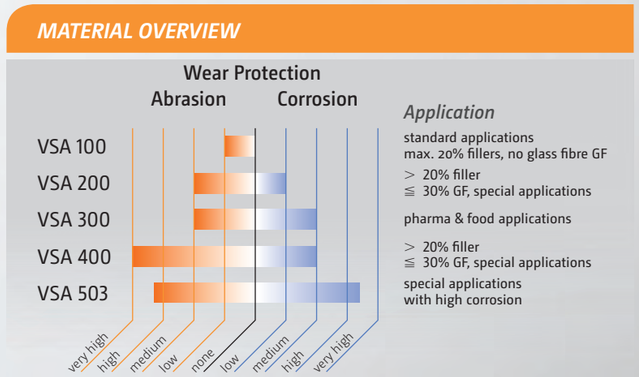
Especially for the wet granulation/-extrusion of liquids ,which act as a binder, injection nozzles are needed. In the simplest case water is used but also different binder solutions like PVP are suitable. For HME processes plasticizer can be added in form of liquids or flavors.

Side feeding

A twin screw side feeder facilitates the feeding of powder into the processing unit of the extruder. Especially for thermo sensitive API's this is an option: The API is fed into the process at a later point in order to reduce the residence time. Also the plastification zone can be avoided which means less shear stress for the API. 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, which 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 kneading. The competence of the Leistritz processing expert is to create the optimum screw design for the respective application.



*LEISTRITZ **ZSE HP-PH***

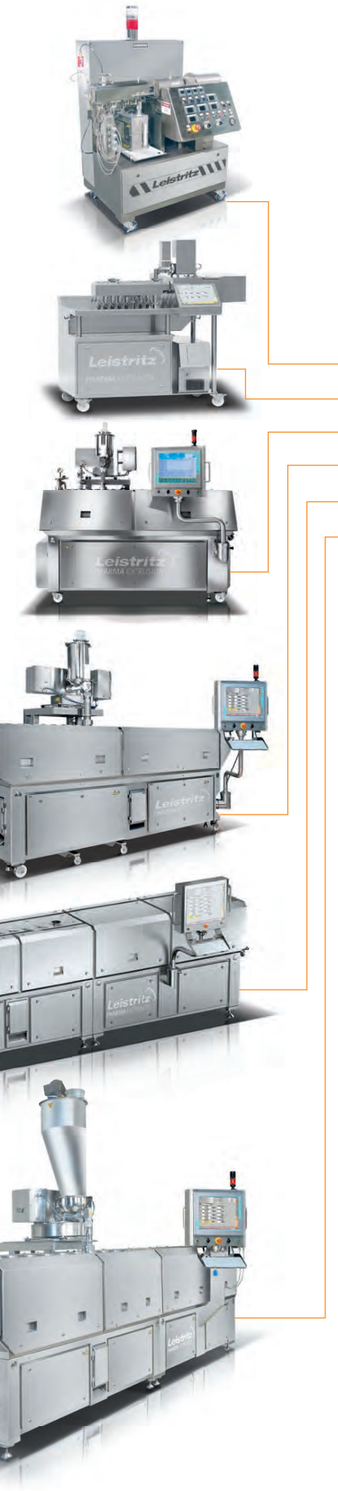
Twin screw extruder overview

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 renown 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

In lab extrusion, the focus is on the optimal adjustment of a process on a laboratory scale, while in production mode high throughputs are desired. During development phase standard processes are negotiable and the extruder must allow the users the same flexibility which they will later find in production systems. With a ZSE 12 HP-PH, for example, small amounts of material can be processed and tested. This comes in particularly handy when using cost-intensive raw materials. The results which are achieved on these machines are the key for the so-called "scale-up" to larger production machines. All Leistritz extruders that are applied in pharmaceutical extrusion from ZSE 12 HP-PH to ZSE 50 HP-PH have the same OD/ID of 1.55. In scale-up, the screw profile of the larger extruder should be similar to that of the smaller extruder. But an identical profile is only a starting point, because adjustments are often needed as mass- or heat-transfer limitations can arise at larger scales, affecting dispersion and uniformity.

» Our machines have the same OD/ID of 1.5: A scale-up from lab to production machines can therefore easily be done. «



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	1,500 x 700 x 1,200
ZSE 18 HP-PH	18	71	1,200	7.1	2,290 x 700 x 1,270
ZSE 27 HP-PH	27	268	500 & 1,200	15	3,650 x 1,150 x 1,800
ZSE 40 HP-PH	40	830	400	37	4,000 x 1,400 x 2,100
ZSE 50 HP-PH	50	1,570	400	70	4,630 x 1,800 x 2,120

LEISTRITZ EXTRUDERS CONVINCE 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

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.

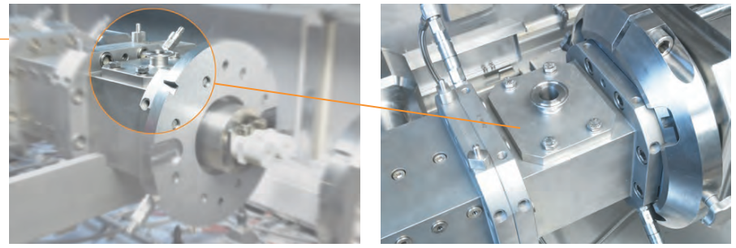
Example of a GMP extrusion line (melt granulation with pellet cooling and transport)

GMP FEATURES

Design highlights

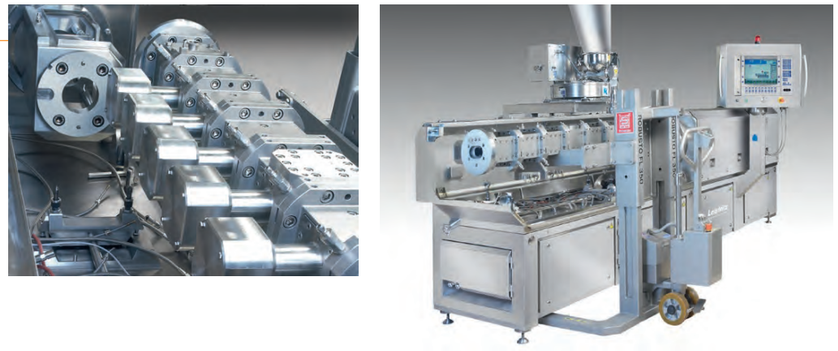
Washing-in-place

The washing-in-place kit simplifies the cleaning. The cleaning tube is plugged to the 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

IP 65 heater shells

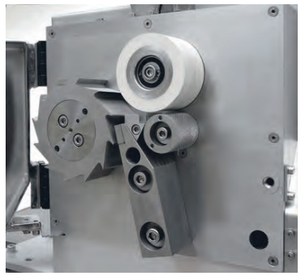
LEISTRITZ EXTRUSION LINES

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 is to use a cooling conveyer belt, where the cooling media is air. A more efficient way of cooling is realized via a water bath (horizontal or vertical). After the cooling and solidifying of the melt, the strands can be cut into cylindrical pellets by means of a strand pelletizer.

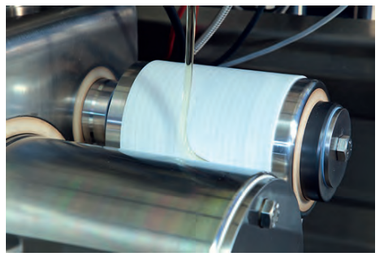


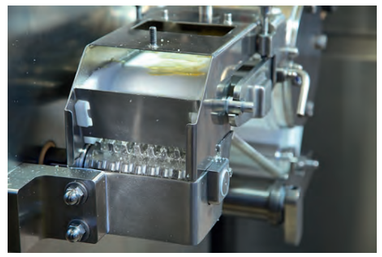
Leistritz ZSE 18 HP-PH with cooling conveyer belt and strand pelletizer for the production of cylindrical pellets

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 only 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.

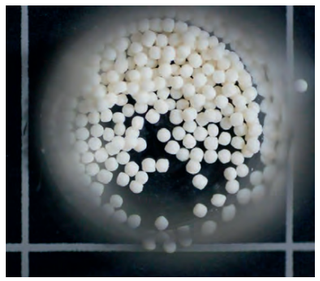
Chill-roll with integrated mill

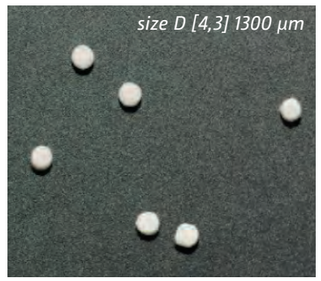




Micro pelletizing

Furthermore, it is possible to cut the melt directly in the hot stage. For example with the Leistritz 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. To get a constant material flow and a narrow particle size distribution one might consider integrating 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.

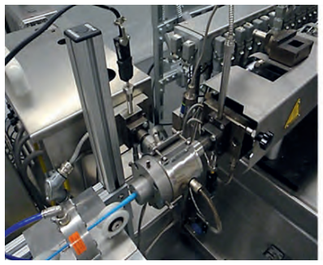


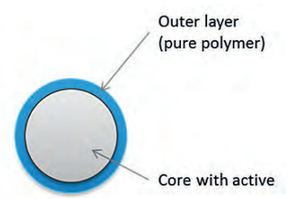


Example of Kollidon SR®-Theophyllin (40%) micro pellets made on a LMP 2.0

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 it is comprehensible that especially the preciseness of the strand diameter is the challenging part in the manufacturing process.





Example of a multilayered, co-extruded strand

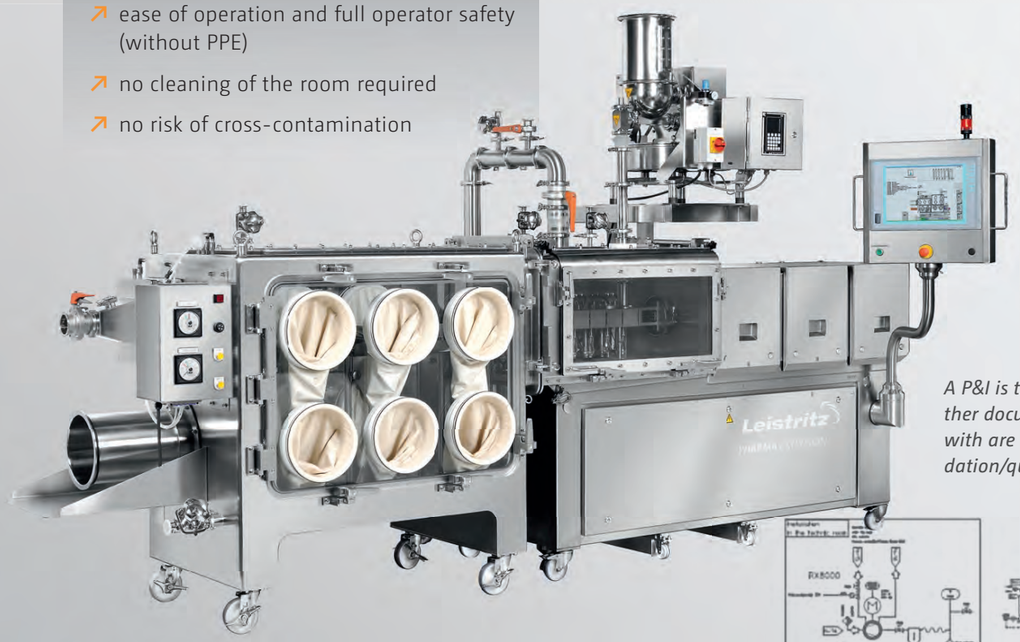
LEISTRITZ CONTAINMENT SOLUTIONS

Engineering know-how

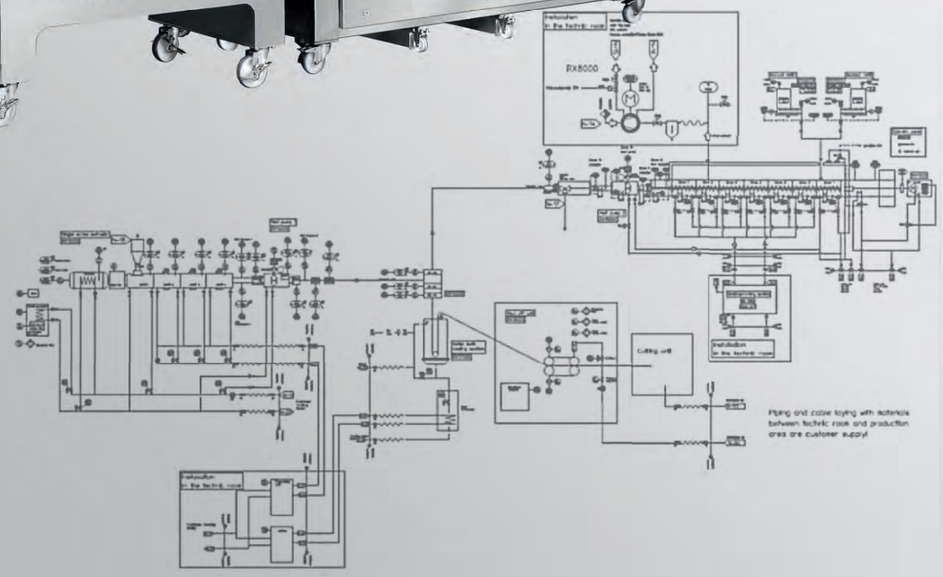
As more and more API's are classified as high hazardous ingredients the operators' safety is a key issue made sure. That shows the need for new designs of extrusion lines as containment solutions which have already been realized by Leistritz for different kind of OEL levels.

WHY CHOSE 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 with are required in the validation/qualification phase.



↗ Plant layout

Extrusion line OEL 5 (<1µg/m³)

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

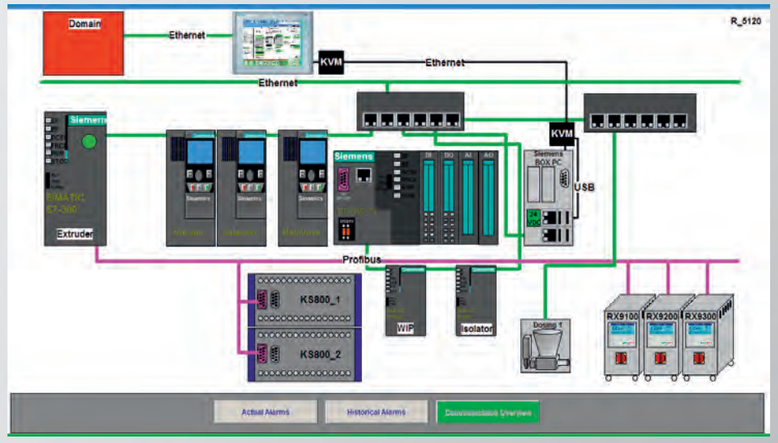
When designing a twin screw extrusion plant all aspects specific for pharmaceutical applications must be taken into consideration. An extruder unites a high level of mechanical standard components and functions with various customized adaptations. The main objective of Leistritz' automation and control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

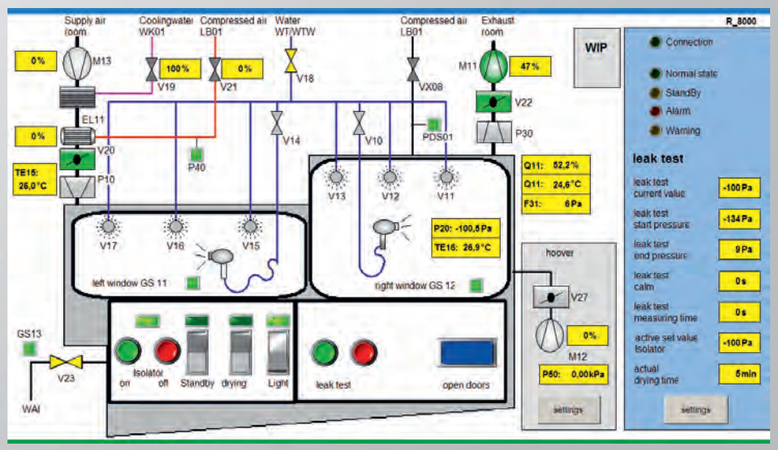
THE LEISTRITZ CONTROL UNIT COORDINATES ALL PROCESSES:

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

With the Leistritz 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. For non-GMP requirements Leistritz offers standard visualization systems based on Siemens PLC.



Example of the line setup

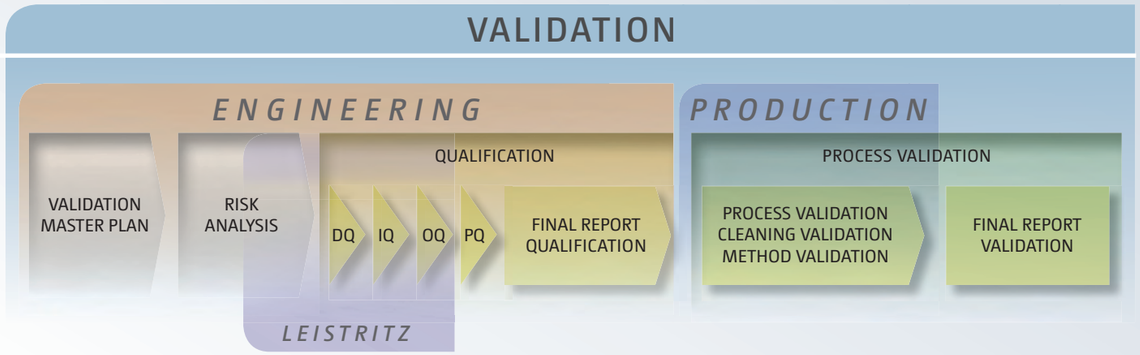


Visualisation example of the isolator

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 (Installation Qualification) and OQ (Operational Qualification).



Overview: engineering and production phase

TYPICAL MILESTONES AND TESTS	
user requirements specification (URS)	user
mastervalidation 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

» As extrusion line supplier Leistritz can contribute a state-of-the-art documentation package. «

TESTING & *OPTIMIZING*

Leistritz extruders worldwide in use

The 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.
In-house, with our laboratories in Nuremberg (Germany) and Somerville (USA) we offer an environment, in which our customers can put their products to the test. Processes are tested, evaluated and optimized here on our lab extruders and equipment.

As the only extruder manufacturer Leistritz offers its customers not only two laboratories for feasibility studies but also a fully equipped development and upscaling center from our cooperation partners. 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 things.

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

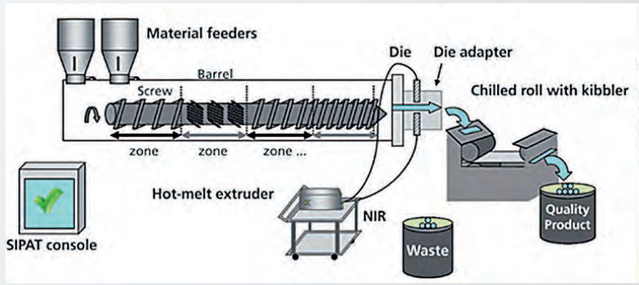
» We accompany our customers throughout the whole development phase: We conduct tests, produce clinical batches in cooperation with institutes and partners or provide rental machines. «

↗ Laboratory work

Process Analytical Technology (PAT)

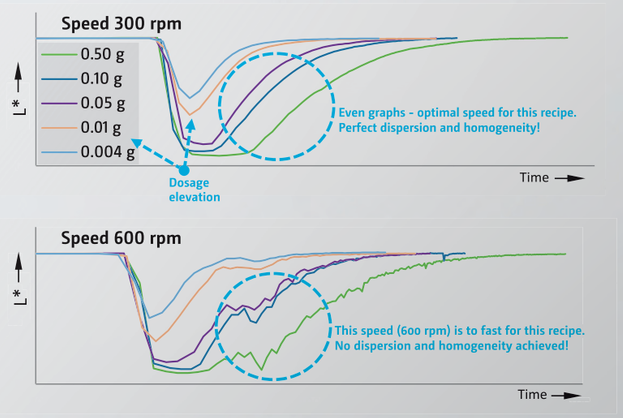
A continuous manufacturing method as extrusion is ideal for a quality by design approach. Based on a risk analysis the critical quality attributes can be defined and continuously monitored. In addition to the typical extrusion process parameters like melt temperature, melt pressure, and specific energy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

Common technologies therefore 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.

SERVICE WORLD

Customer care & consulting

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. One of the formulas to stand one's ground in the tough competition is to work in an efficient and economical manner. Be assured by our technical support with its long experience in dealing with extruders and extrusion lines. Our team is active around the world for you – competent and solution-oriented. It makes sure that your technology always keeps on running.

OUR SERVICE OFFERS:

- ↗ assembling/commissioning
- ↗ revamping
- ↗ original spare parts
- ↗ trials in our pharmaceutical labs in Germany and USA
- ↗ consultancy in the field of process engineering
- ↗ training sessions, also tailor-made inhouse
- ↗ 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. «

*LEISTRITZ **TWIN SCREWS***

Now and then

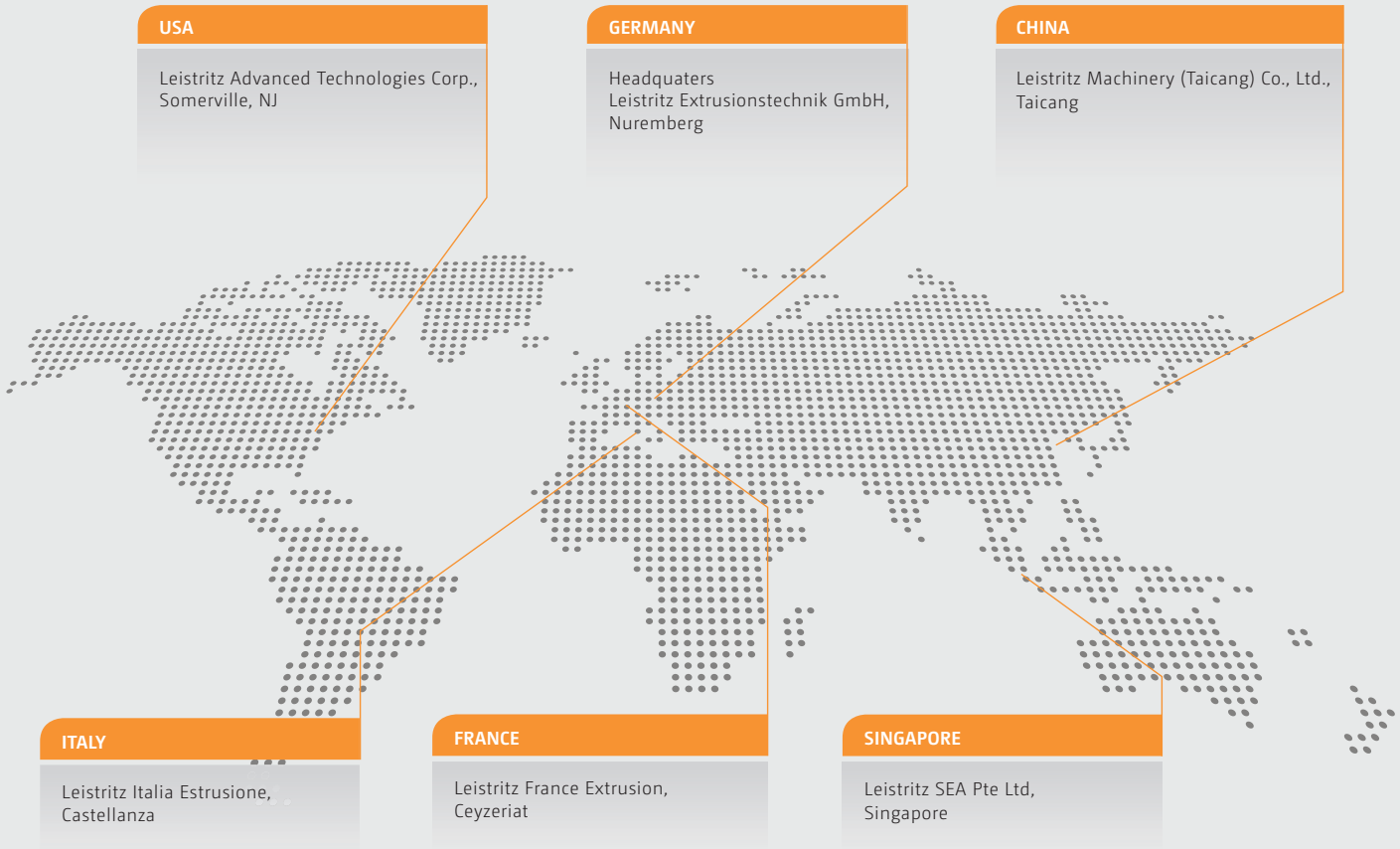
Developed almost 100 years ago for food and natural rubber/plastics applications, nowadays twin screw extrusion generates some of the most cutting-edge drug delivery systems available. Processing with twin screws offers significant advantages as compared to batch manufacturing techniques. An advantage 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 manufacturer to develop twin screws for this application field. In the meantime technology has immensely improved.

What is occurring today for pharmaceuticals with regard to the implementation of extrusion technology to increase efficiencies and save costs is analog what occurred approximately 80 years ago in the plastics and food sectors of industry as batch processes were replaced by continuous manufacturing alternatives for reasons that are obvious. 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.

EXTRUSION TECHNOLOGY

Available for you all over the world



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