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# COLLIN TECHNEWS

COLLIN – TECHNOLOGY MAGAZINE

MEDICAL·LINE

# PHARMACEUTICAL, MEDICAL & PLASTIC TECHNOLOGY

## A successful symbiosis

## All-in-one solutions for the development and production

## Design Guidelines

## Validation

NGA

# EDITORIAL

DI Dr. Friedrich Kastner
*CEO / Managing Partner*
*COLLIN Lab & Pilot Solutions GmbH*


Dear Readers,

In recent years, our sector has been criticized unjustly, however, in some cases also justly. Many media reportings have reinforced the opinion and image formation of the broad public. However, especially the last year showed to many people how important plastics are in our life! Starting with protective shields, masks, protective clothing, breathing hoses, injections right through to closing caps for vaccination ampullae. All these products are made of plastics and nobody wants to live without them because they show the variety, possibilities and positive aspects of polymers.

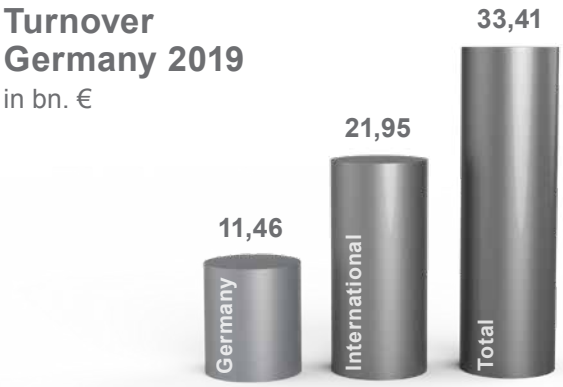
Nowadays, the medical and pharmaceutical sector simply cannot be imagined without plastics! Here, COLLIN comes into the picture. Because as international pioneer, we have been drawing on decades of experience and know-how in the development as well as the production of extrusion lines for laboratory and production. Together with our subsidiary COMELT – specialised in extrusion dies – we provide our worldwide customers in the medical and pharmaceutical sector with our machines. They use our solutions for the production of medical or pharmaceutical products.

Whether drug-loaded strands, films for infusion bags, dialysis or catheter hoses, medical yarn, wound dressing material or fleece for the production of protective masks – products made of plastic have revolutionized the medical sector.

Read more about the symbiosis of medicine, pharmacy and plastics in our current issue of our COLLIN TECHNEWS!

Friedrich Kastner ■

# CONTENTS




3.1, Source: SPECTARIS, Statistisches Bundesamt, Eurostat

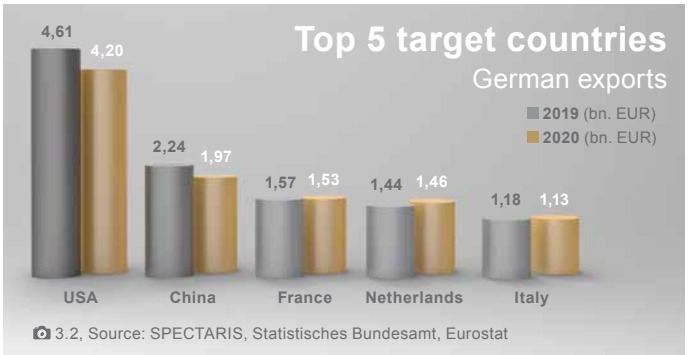
# PHARMACEUTICAL, MEDICAL AND PLASTIC TECHNOLOGY

## A successful symbiosis

Author: Dr.-Ing. Franz Grajewski

**In 2019, the global market for medical products included 445.5 Mrd. $, with a growth of 5.6%. 39.2% of it represent North America, 27.9% Europe, followed by Asia / Pacific with 25.9% /1/. Including 33.4 Mrd. $ generated by Germany, see image 3.1, /1/.**

It is remarkable that in this sector, there are mainly medium-sized companies and that R & D with 9% is well above the average of German industry. The reason for this high percentage of KUM in this sector is probably that small companies can more quickly react to new trends than a big group can do. With an export rate of 66%, Germany is established with its products worldwide. The 5 most important markets can be seen in the graphics 3.2.




3.2, Source: SPECTARIS, Statistisches Bundesamt, Eurostat

In this context, it can be seen that COLLIN Lab & Pilot Solutions as highly flexible, innovative and worldwide acting company is ideally positioned in this important industrial sector.

Already in the 1960s, first ideas for combining plastics with pharmaceutical agents were published. The oral administration of medicine requires that it is water-soluble. Modern agents fulfil this requirement either only to a very limited extent or not at all. So already in 2015, more than 40% of the newly developed agents were not water-soluble /2/. Also due to the enormously increasing cost pressure, new agents and processing methods had to be developed. At the same time, advantages of extruded products for medical applications and devices were recognized and realized in a variety of different products. Drug-loaded materials are subject to strict rules regarding accuracy of the quantity of drugs, homogenous distribution and constancy of the delivery rate in the body. New administration forms, which are based on diffusion processes from the carrier into the body were developed. Thus, there was the possibility, by controlling the diffusion speed, to achieve a constant delivery of the medicine for days, weeks or even months. The important influencing factors are the diffusion behaviour of the active agent in the polymer and the concentration but also the geometric marginal conditions such as diameter, layer thickness of membranes, their positioning in the overall structure and the surfaces /4/. It is obvious that narrow tolerances are required.

In the early 1990s, by FDA (Food and Drug Administration, USA) and EMA (European Medicines Agency), the term QbD (Quality by Design) was coined and incorporated in the regulations for development and production of drug-loaded pharmaceutical products. With this process, the manufacturing process comes to the fore, of course. Two essential process steps are the incorporation of the agent into a carrier matrix and the forming of the geometry of the administration form (tablet, implant). Both are decisive for quality and uniformity of the agent delivery in the body.

Normally, the processing steps were made in a batchwise way. It is known that such transient processes »

show significant disadvantages regarding homogeneity of the distribution within the product and quality of the product from batch to batch. In order to overcome these problems, considerable economical and organizational efforts are necessary.

Already at a very early stage, industry and approval agency have recognized that the continuous production process is the only advantageous alternative. Already in the early 1990s, FDA and EMA required continuous processes. Thus, the introduction to extrusion technology as economical and high-quality procedure was strongly expanded. Particularly from 1990 to 2006, the number of patent applications in this sector had increased by a factor of 10 and this growth rate has been increasing continuously /7/.

If the advantages of extrusion are summarized, the following picture emerges:

- Optimal homogeneity
- Wide range of process temperatures (RT up to 300°C)
- Exact temperature control in each heating zone
- Short residual times in each process step
- Short product change times
- Stable, stationary, continuous processes
- Constant product quality during the entire production period

Already in the highly innovative early phase, with the development of a shaping calender for pharmaceutical products, COLLIN Lab & Pilot Solutions, together with the company Abbott, entered the medical sector as successful manufacturer. On the following pages we will provide you with an outline of the most important product classes in which COLLIN Lab & Pilot Solutions acts successfully. ■

# Drug-loaded strands

The birth of the so-called intravaginal rings (IVR) was in the 1970s. Already in the late 1960s, the first patent application was filed /3/.

However, it took 30 years after the first rings were introduced in the market.

According to /4/, there are 4 designs of rings.

- Reservoir ring consisting of a core including an API (active pharmaceutical ingredient) and an outer membrane layer.
- Matrix ring consisting of a strand filled with API
- Sandwich ring with an unloaded core, one layer with API and an outer membrane
- Chamber type with a carrier ring with chambers in which carrier polymers filled with API are integrated. Here, different APIs are possible.

The first applications were birth controls. Today, IVR, which not only are used for contraception but which also contain layers with anti-venereal disease medicine and / or anti-HIV /4/ are currently being developed. EVA and TPU have proven to be polymer carrier in this field.

For some time, research has been carried out on mini-implants, which are also API carrier /11/ for the treatment of certain eye diseases. One possibility are mini strands consisting of a core (API loaded) and a membrane. Core diameter < 300µm, membrane thickness < 50µm and shrinkage behaviour put special requirements on extrusion technology. ■

# Bioresorbable and biocidal compounds

First, in the early 1970s, bioresorbable materials were used in surgery as suture material. Still today, that is an important field of application. The materials used today are PolyL-lactide (PLLA) and Polylactide-co-glycolide (PLGA), Poly DL Lactide (PDLLA) /5/. One of the most important advantages of the implants, degradable by the human body, is that after healing, the surgical removal of the implant is not needed. However, the polymer materials of today do still have an essential disadvantage compared with other materials. The tensile strength is not enough for the use in load-bearing areas. In order to improve this condition, fillers are used /5/. Although, a number of implants is successfully used, further research regarding material optimization is required. For example, suitable fibres could strengthen the implant and, in some circumstances, stored in the bone. It is obvious, that suitable machines must be available for that.

Especially in the clinical sector, it happens more and more that resistant and partly-resistant germs colonize plastic surfaces and form bio films which show high tolerances regarding common surface cleaning methods or disinfectants. For applications in medical institutions, devices or in the body, this is not tolerable. The antibacterial effect of, for example, silver resulted in the development of special masterbatches in order to protect plastic surfaces. A number of other additives with this characteristic are under development.

In this process, the mixing of plastics with fillers in powder form, short fibres, liquids or additional polymer types as well as agents is very important. Since these are normally very expensive, it is attempted to achieve meaningful results with as little material costs as possible. The scalability from the small developing machine to production volume is also required. ■

# Functional hoses

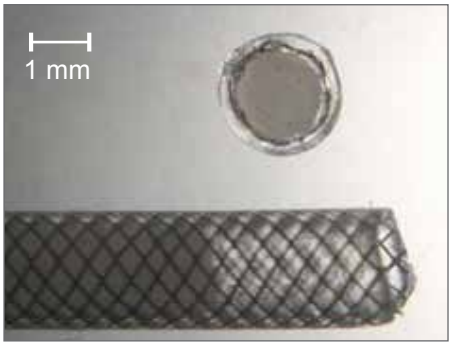
In medical technology, a huge variety of hoses is used. With different functions, they are used in different medical devices, but also in the body of the patient. Alone of the range of diameters from <=500µm to >=6000µm, there is a wide range of technical challenges in production. The materials used, for example, silicone, PEBAX, PFA, TPU, TPE, LDPE, PA, PTFE, PVC, etc. are just as demanding. Since, normally, only one plastic cannot fulfil requirements specification, coextrusions often used. Layer thicknesses in the extruded material of <100µm are not uncommon.
For example, for a layer thickness of 100µm with an inner diameter of 600µm and a standard density, for a take-off speed of 100m/min, the throughput for the extruder is 21g/min.
This simple numbers game demonstrates the essential requirements on a hose line:

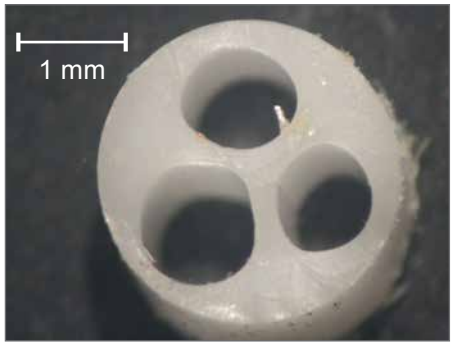
- Precise output of smallest throughputs in the extruder
- Absolutely continuous speed distribution at the die outlet
- Most accurate control of the take-off speed
- High cutting speed for cutting the hoses
- High-performance device for removal and storage

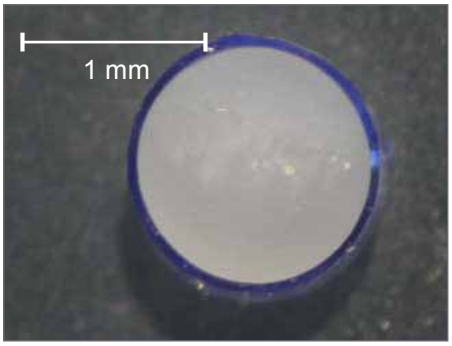
In this product segment, COLLIN Lab & Pilot Solutions has successfully been acting for years.

The reasons are:

- Know how in dimensioning of screw – also for mini extruders
- Dimensioning of the flow channels in the dies.
  Here, it should be noted that the adding of agents can considerably change the flow behaviour compared with basic polymer. Therefore, for the design, it is very important to use a real viscosity function (with API).
- Sophisticated control for controlling all line components at high take-off speeds »




The images with a selection of multi-lumen hoses show further examples for the challenges of the machine manufacturer but also of the extruding company.

In addition to the desire for several channels in one hose, there are also requirements for changing mechanical characteristics in axial direction of the hose. These are the variation of the bending stiffness and strength in radial direction. This is achieved by positioning layers of different numbers and thicknesses in a fixed sequence along the hose. State of the art is that hoses with the required diameters are extruded. Then, these are, depending on the layer design, manually placed and shrunk together. This uneconomical procedure requires a continuous process. Ideally, it should be a one-step process. COLLIN Lab & Pilot Solutions is working on an extrusion solution which can be introduced to the market in the near future. ■

## Films for medical & pharmaceutical applications

Films are used as packaging material up to high tech carrier films for electronic components, which are applied as plaster on the body. By means of special print processes, with conductive polymers, electronic components are integrated in the film, which analyse different body functions. Also for analysing purposes, the „Lab on Chip “technology was developed. Films are equipped with micro channels, in which liquids, because of the capillary effect, are transported to analysing stations, which are on the chip. For this procedure, only lowest quantities of liquid are required.  A big advantage is the low space requirement. »

The materials used comprise the full spectrum of materials of which films can be extruded. At this point, the entirety of requirements cannot be described.

The most common are:

- Mechanical characteristics
- Abrasion resistance
- Printability
- Sterilizability
- Transparency (also mat)
- Weldability
- Defined barrier characteristics against different media
- Breathability
- Biocompatible for the use on or in the body

This can only be achieved by co-extrusion. The trend goes up to 11 layers in one film. Correspondingly, the line for the production is very complex. Furthermore, cleanroom suitability and high flexibility for product changes are important since small lot sizes must often be available very quickly.

The COLLIN Lab & Pilot Solutions technology for flat films and blown films is exactly in this field and has been used worldwide for many years.

Today, COLLIN Lab & Pilot Solutions machines and lines are used for:

- Drug incorporation in carrier materials (waxes, cellulose, starch and polymers)
- Degassing of volatiles
- Pelletizing of pre-mixtures for tablets
- Continuous tablet shaping
- Coating of drug-loaded films for external skin applications
- Coextrusion of drug-loaded strands for implants under the skin
- Production of mono and multi-layer resp. mono and multi-lumen catheter hoses
- Production of mono and multi-layer films for infusion bags ■

# ORGANISATIONAL CONDITIONS

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5126 S Royal Atlanta Dr. Tucker, GA 30084, U.S.A

**QUALITY MANAGEMENT SYSTEM**
complying with the requirements of standard
**ISO 9001:2015**

Development, production, service and sales of laboratory and pilot equipment for plastic testing and processing.

Registration No.: 18445/0
Date of initial issue: 17 November 2016
Valid until: 15 September 2022

The validity of the **quality**austria certificate will be maintained by annual surveillance audits and one renewal audit after three years.

Vienna, 23 August 2019

Quality Austria - Trainings, Zertifizierungs und Begutachtungs GmbH,
AT-1010 Vienna, Zelinkagasse 10/3

Konrad Scheiber
General Manager

Dr. Mag. Anni Koubek
Specialist representative

The current validity of the certificate is documented exclusively on the Internet under http://www.qualityaustria.com/en/cert EAC: 18

Companies, which are active in the medical and pharmaceutical sector have to receive and periodically present high-quality and organizational standards.

Since the mid-1990s, quality management systems according to ISO 9001 have been introduced and are now established as standard tool for controlling the quality of all processes of a company.

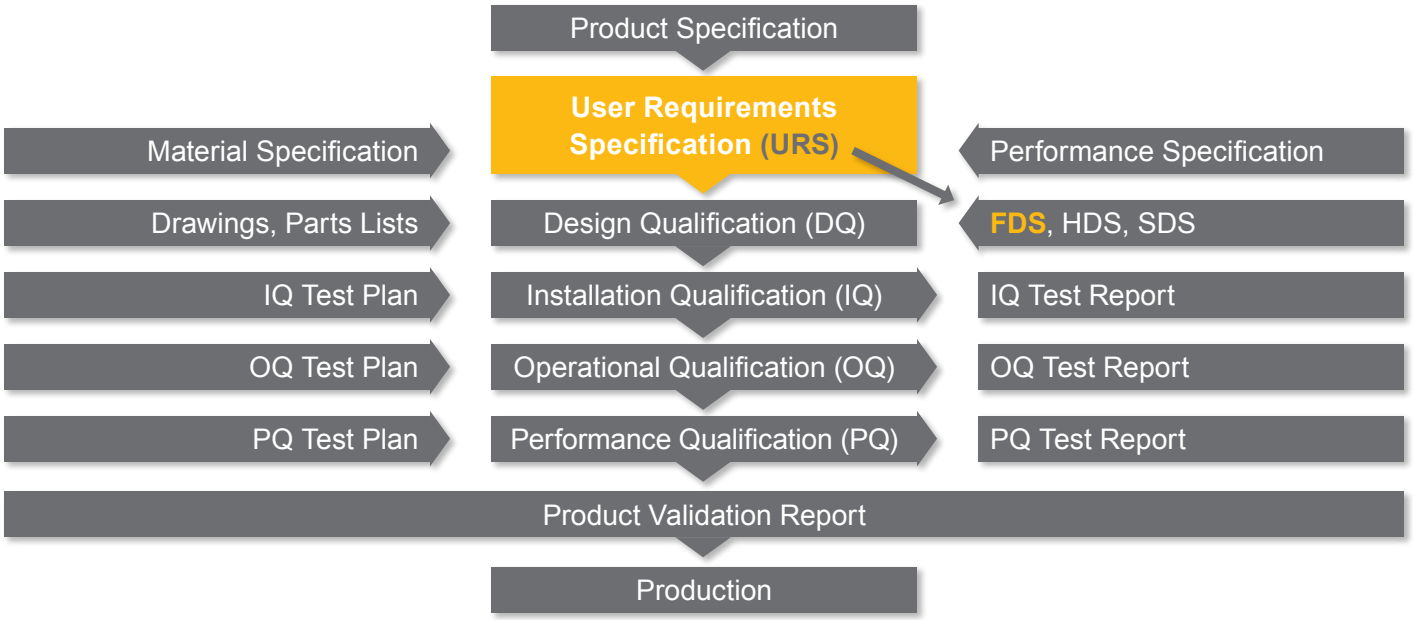
In 2009, COLLIN Lab & Pilot Solutions proved to have implemented the regulations of ISO 9001. Since then, all departments of the company act accordingly.

Important tools are:

- Design reviews, from a certain design progress with the customer
- FMEA (Failure Mode and Effects Analysis)
- Risk assessments

Linked to this is a continuous improvement process (KVP); the compliance is strictly monitored by the management. ■

# Good Manufacturing Practice (GMP)




COLLIN Lab & Pilot Solutions has a specially trained team to follow the FDA guidelines in the phases

- design
- production and installation
- qualification and validation
- documentation

for the manufacture of pharmaceutical and medical extrusion lines. The basis for that is the illustrated „Validation Master Plan “VMP (taken /9/).

The VMP describes procedure and responsibility during the line qualification as well as the process validation.

Moreover, it describes the responsibilities, definition of the validation volume, validation priorities, documentation contents and filing of approvals and signatures.

Important terms:

- **URS** = User Requirement Specification
- **FDS** = Functional Design Specification
- **HDS** = Hardware Design Specification
- **SDS** = Software Design Specification
- **DQ** = Design Qualification / Design Freeze
- **IQ** = Installation Qualification
- **OQ** = Operation Qualification
- **PQ** = Product Qualification ■

# User Requirements Specification (URS)

| Initial Requirement Description | Type of failure | Cause of failures | Conse-quences of failures | Existing control | Influence on quality | Qualification category (Comm./Qual.) | Test ref. |
|---|---|---|---|---|---|---|---|

The URS has the key importance. It represents the requirements specification and contains product specification, material specification and performance specification. A section of how it is defined by COLLIN Lab & Pilot Solutions can be seen in the image. ■

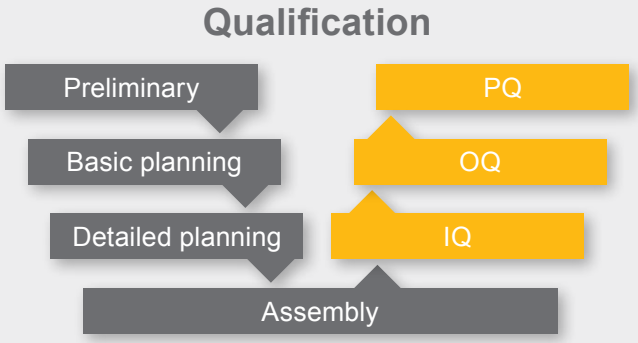
# Design Qualification (DQ)

The design qualification contains the function qualification, hardware specification (electr.), software specification as well as all drawings and parts lists.

The following qualification scheme /9/ shows the basic and general procedure from design qualification up to product qualification. The qualification guarantees that the line and the process have been realized in accordance with the specifications and that the requirements of the requirements specification are fulfilled permanently.

Prior to performing, qualification and validation plan have to be approved by signatures after fixing. ■

DQ-Design Qualification




# Installation Qualification (IQ)

For the machine and line manufacturer, the installation qualification is very important. It is the documented evidence that the line has been installed according to the specifications, requirements specification and other applied standards. Normally, it includes evidence about:

- Supplier audits as well as factory acceptance tests
- Visual inspection of the rooms, comparison with drawings, data sheets etc.
- Instrumentation as specified
- Data sheets, material certificates, test certificates
- Operating and maintenance manuals. These have to be provided prior to delivery. ■

# Project documentation

Obviously, according to the VMP, a comprehensive and exact documentation of all process steps and the results achieved is required. Furthermore, appearing deviations and their corrections are determined. For that, COLLIN Lab & Pilot Solutions has prepared detailed plans /9/.

The essential elements are

- Complete documentation of the customer communication
- Description of all specifications
- Definition of the project team
- Risk assessment
- Conditions for acceptance (FAT, SAT)
- Modification management
- Operating instructions
- Assembly protocols ■

# COLLIN LAB & PILOT SOLUTIONS DESIGN GUIDELINE ACCORDING TO GMP

**The design of our lines for the medical sector is subject to strict internal rules. These comprise the clean-room suitability (class 7 and 8), easy access to the line components and reliable cleaning, software and control.**

## Cleanroom suitability

The requirements according to DIN ISO EN 14644-1 require a minimization of the generation of particles by lines operated in the cleanroom. Essentially, that involves the avoidance of abrasion, dust generation, exhaust generation, etc.

That results in considerable, partially very expensive measures at the machines.
COLLIN Lab & Pilot Solutions realizes them by

- Special steel for all product-carrying parts
- Special plastic for product-carrying parts
- Special, approved lubricants
- Machine frames made of stainless steel
- Stainless steel covers closed as completely as possible
- If approved, parts, which are not carrying products are covered with special coatings. In any case, they have to be resistant to detergents.
- Only water-cooled motors
- Liquid-tempered extruder cylinders
- Cable guiding in stainless steel design and closed
- Bearing completely closed and equipped with especially approved lifetime lubrications
- Cables and hoses must have a smooth surface ■

## Accessibility and cleaning

Lines for medical and pharmaceutical production are subject to strict cleaning instructions. Not only special detergents are prescribed, also cleaning cycles can be very short, depending on the products. Therefore, COLLIN Lab & Pilot Solutions takes special account of the wish for easy access and cleaning.

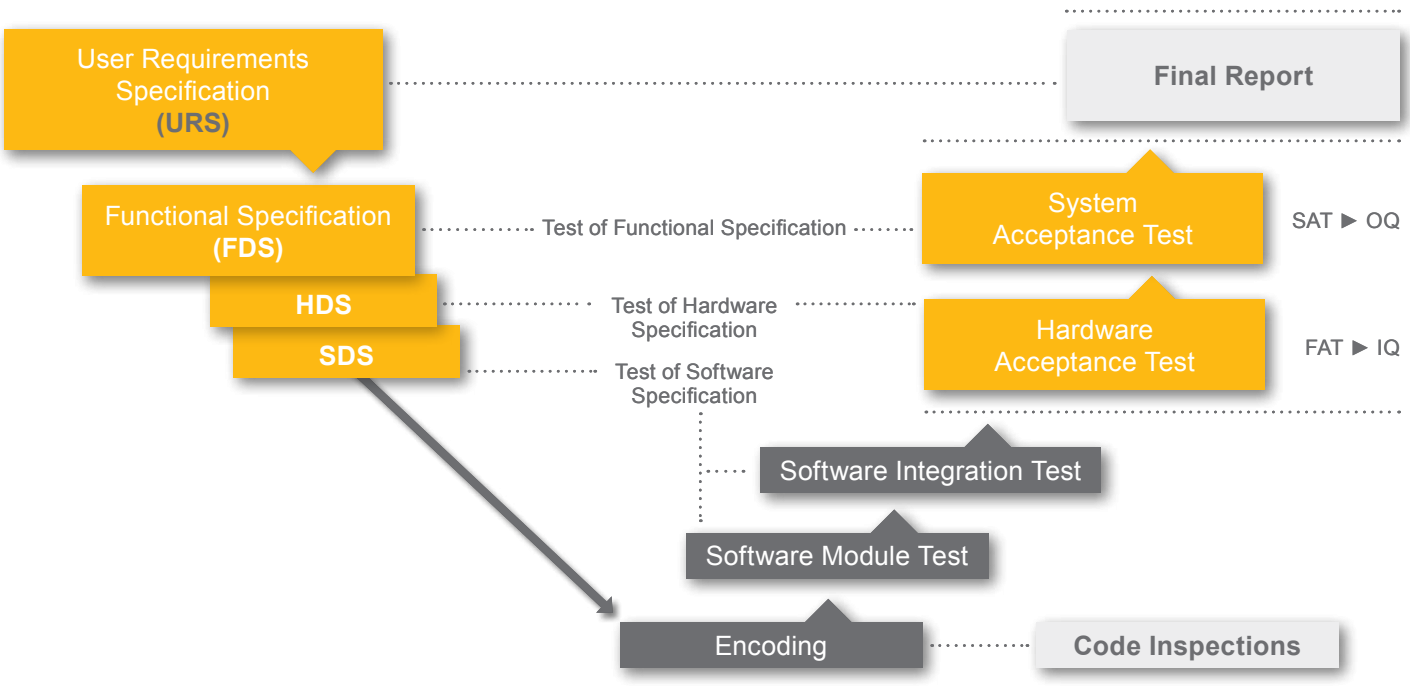
The most important measures are:

- All external surfaces consist of polished stainless steel, as alternative, special coatings are used
- Sharp corners, grooves and undercuts have to be avoided
- Corners have to be rounded with, at least, R=6
- Surfaces formed in order to avoid that detergents reach product-carrying areas
- All product-carrying parts have to be dismounted quickly and easy
- Detergents have to be removed from the surfaces completely
- Machine feet must be designed in such a way that impurities do not accumulate

The picture shows a design example. As option, especially for cleaning the screws of compounders, there is a motor-driven traversing possibility of the drive unit available which allows quick access to the screws. ■

# Design rules for control software according to 21 CFR, Part 11

Also for the preparation of the entire computer environment, the URS is decisive. FDS, HDS and SDS result from it. According to them, the SW code is generated, followed by a SW module test. Their integration in the system is checked according to the specifications. Hardware and system acceptance tests are documented with a final report.




When programming the software, a variety of safety regulations has to be ensured which guarantees that data abuse or manipulations, in whatever form, cannot occur. It has to be observed that a complete, comprehensive documentation is given by the software. »

The most important principles are:

- Effective protection against system access with an access hierarchy and electronically coded signatures
- All process data must be stored electronically and on paper
- All files must be protected against manipulation
- Hardware, control systems and processes must be checked
- The use of audits generated by computer, monitoring according to a fixed schedule
- Access to system files and validation documentation by FDA inspectors
- Written standards for SW development
- Definition of apprenticeship and qualifications of SW developer
- All system modifications must be documented by electronic signature

The machine and line control of COLLIN Lab & Pilot Solutions is subject to these procedures and principles. Their philosophy is based on the requirement to achieve flexibility as high as possible. Especially during tests, it is necessary to vary the line configurations. That means, line components, e. g. extruders shall be exchanged and / or removed resp. added quickly and easy. For this reason, all machines are equipped with an autarkic control.

The image 13.1 shows the touch screen of the HMI of a compounder. The ergonomic design and the display of machine parameters allows the operator to get an optimal overview and to modify individual parameters quickly.

Via tabs, e. g. current temperatures of the heating zones, absolute deviation of set values or the deviation in percentage terms can be recalled.

All compounder components such as main feeding, side feeding as well as gear pump are displayed. If all parameters such as speed, throughputs (if necessary gravimetric) are pre-set, the mode pressure-speed-control of the machine can be pre-set.

If all running conditions of the machine are pre-set and the product corresponds to the pre-settings, all extruders and downstream equipment are coupled at the given line speed. The image 13.2 shows the example of a 7-layer calendering line. Via tabs, the operator can select each


13.1


13.2

machine within the line and can enter the parameters of every component at every machine of the line.

The concept guarantees highest operating comfort and avoids input errors. These easily occur if the operator has to approach every single extruder for input the data. After coupling, the line speed can be decreased as well as increased by ramps.

The superordinated software FECON is the central control of the line. It allows the input of „recipes “, which comprises the entire set of parameters with which the line shall be run. These are stored in the system and can be recalled at any time. With this procedure, regarding the documentation of a test, test repetitions and modifications of just single line parameters, an enormous time saving is achieved. FECON stores all test data and offers comprehensive trend analysis and graphic representation of the results.

The possibility of a pre-heating automatic system saves valuable test or production time since the line, e. g. overnight, will be kept at a low temperature level and, before starting production, it will be heated up again to achieve the set level of temperature. Safety precautions such as heating current monitoring avoid uncontrolled temperature modifications. Should – for whatever reason – a zone temperature exceeds a maximum value, the entire line will be switched off. ■

# Calculation possibilities of COLLIN Lab & Pilot Solutions

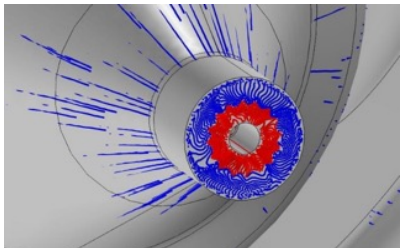
As recently as 10 years ago, the design of flow channels in extrusion tools was totally depending on the fine feeling, experience and patience of the toolmaker. This „Trial and Error “procedure was most often time-consuming and expensive. As you can see in the above product examples, in medical technology, always small dimensions are used, which, furthermore, are very narrowly tolerated. This requires exact knowledge of the flow in a tool. Not only loss of pressure and throughput (line speed) have to be compatible.  Especially in coextrusion, flow speed and viscosity have to match when layers meet. If this is not the case, turbulences occur, which avoid a clear separation of the layers and an exact thickness. Moreover, it is absolutely necessary that the output speed of the product is equally distributed over the cross-section.

In order to avoid these difficulties and a long start-up of the die, COLLIN Lab & Pilot Solutions uses the possibilities of FEM (Finite Elements Method). An experienced team designs flow channels for all tool types and makes cooling calculations for cooling baths and cooling rolls. Thus, beforehand, optimisations can be achieved. Due to many years of experience, the accuracy of theoretical statements has enormously increased and is very reliable. This will be shown by the two following examples.

Not only the procedural and mechanical dimensioning of all dies is made at COLLIN Lab & Pilot Solutions. The manufacture of tools is made by the subsidiary COMELT with state-of-the-art processing centres in air-conditioned rooms.

Task 1 was a two-layer hose with an outer diameter of 1.5 mm and an inner diameter of 350 µm. The inner layer should have a radial shape in outward direction. The required total throughput was approx. 9 kg/h.

The following image 14.1 shows the calculation result at the outlet of the die after several optimization steps. It is clearly visible that the radial geometry should be very clear. Next to it, there is a microtome section 14.2 of the extruded profile, run without additional rework at the flow geometry.



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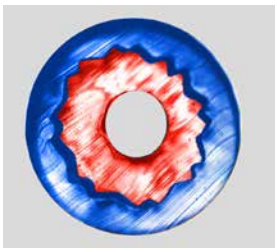
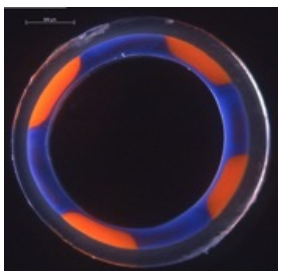


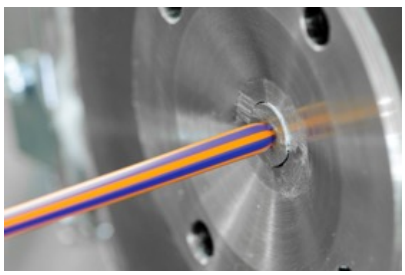
14.2

In many cases, it is necessary that the doctor can see the way of the hose in the body on the X-ray screen.  For this purpose, hoses are equipped with strips, which contain an X-ray contrast medium in the polymer. The number varies from one strip up to four. COLLIN Lab & Pilot Solutions has optimized the flow geometry for a hose (Da 2mm) with four strips (width 100µm) and calculated the following result (image 14.3). The picture 14.4 shows the hose at the outlet of the die.

Exchangeable mouth piece and mandrel geometries allow the die to produce blown films with inked strips in longitudinal direction. The strips can e. g. be inked white, in order to receive a better readability on the packaging, in case of a sufficiently large transparent sections to visually assess the content. ■



14.3



14.4

https://www.collin-solutions.com/en/product/extruders-medicalline/

15.1

# MACHINE AND LINE TECHNOLOGY FOR MEDICAL AND PHARMACEUTICAL APPLICATIONS

**The wide range of know-how of COLLIN Lab & Pilot Solutions in handling the comprehensive guidelines for design and construction is reflected in the design of lines for nearly the complete range of extruded products. The examples below will give an idea of the product portfolio of the company.**

## Single-screw extruders

Also the extruders for medical applications are characterized by their compact design and flexible use. The series is offered with the Types E12P, E16P, E20P, E25P, E30P, E45P and E60P. Thus, each desired performance range, both, for development and production, is covered. The machines meet the rules according to FDA 21 CFR, ISPE, ISO 13485, Din EN 10204/3.1B, cGMP/GMP. They offer an extremely compact design and are subject to hygiene regulations.

Different drive concepts (AC induction motor, high torque motor) are available. Depending on the design, speeds of up to 450 min-1 are possible. The speed accuracy for inductions motors is +/-0,5% and +/-0,25% for torque motors. Thus, also in the lower speed range, very low throughput deviations are guaranteed. Combined with correspondingly designed gear pumps, also for smallest dimensions of the extruded material, the exact throughput with highest accuracy can be run.

The extruders are suitable for all materials, which are used in this field. Screw geometries, designed for the respective application are available. The machines are designed for a counter-pressure of up to 415 bar. If the value is exceeded, the machine will be switched off by software. Should this type of shutdown fail, there is a safe hardware shutdown at 560 bar, according to the standard specifications.

The image 15.1 shows the cGMP machine, which is, as far as technically possible, mostly made of stainless steel. There is also a type of where product-touching parts are made of stainless steel and all other covers and machine frames are coated. Here, special coatings are used, which are resistant to cleaning procedures on a permanent basis. ■

https://www.collin-solutions.com/en/product/compounders/

16.1

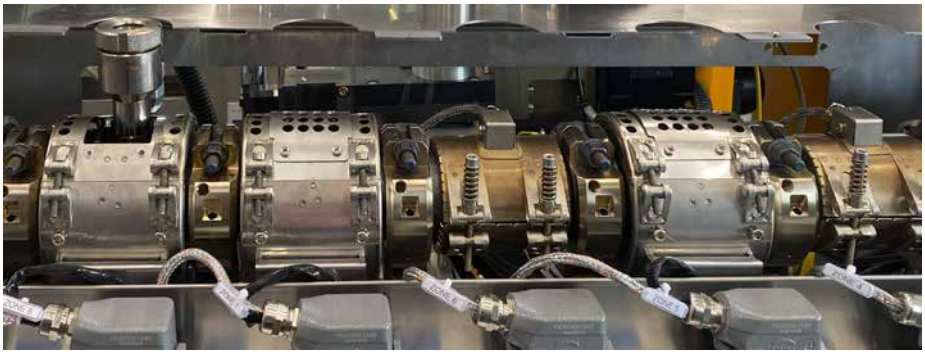
# Compounders

The COLLIN Lab & Pilot Solutions compounders are subject to the same design guidelines like the single-screw extruders. Due to their high flexibility, they can be used as processing and mixing extruder in pelletizing lines, but also as direct extruder, integrated in lines for the production of end products. The use as direct extruder in combination with a shaping calender results in a very economic production for continuous tablet production. The series includes ZK12P, ZK25P and ZK35P. The compact design allows very short product change times as well as quick and easy cleaning, so that hygiene regulations are fulfilled. Design and construction are subject to the same strict rules, which also apply for the single-screw extruders. The Medical Line compounders (ZK25P, ZK35P) picture 16.1 convince by their high torque density, which allows the processing of all highly viscous and highly-filled polymers. The machines run with a maximum speed of 1200 min-1.

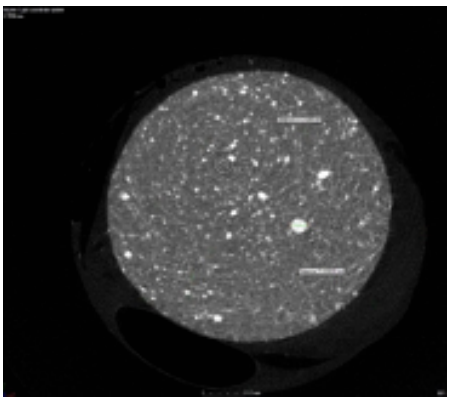
Depending on the mixing task (number of polymers, additives, etc.), processing lengths of 36D to 60D are possible. The modular design of the screws allows an optimal configuration of the processing sections regarding dosing of additives and fillers, mixing zones and discharge zones.

A ZK25 is pictured. Easy access to all surfaces is quite obvious. The drive is completely sealed. The switch cabinet below the processing part is hermetically sealed, so that inside, harmful or even toxic substances cannot accumulate. This circumstance serves the security of the maintenance personnel.

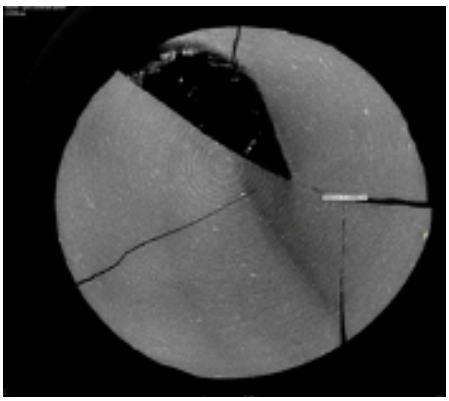
The complete decoupling of the gravimetric dosing devices from the rest of the machine is also remarkable. This ensures that even smallest vibrations do not influence the discharge accuracy. Especially in case of small throughputs, that is an important aspect.



16.2



17.1



17.2

The cylinders consist of elements with a length of 6L/D. The picture 16.2 shows a design example of a ZK25P. The cylinder elements are connected with heated C-flanges. In this way, they can easily and quickly be positioned at different positions, for example if the screw configuration has been changed. They are – thermally separated – mounted on a rail so that the cylinder as a whole, either manually or by motor, can be removed from the processing unit. Thus, the screws can easily be cleaned.

Due to economic considerations, for the development in pharmacy very small test quantities are desired, since one kilogram can easily cost several thousand Euros. Therefore, the desire for batch weights of approx. 50g - 100g is very great. In addition to meaningful mixing results, a test machine should allow quick product changes, quick cleaning and easy and safe handling by the test personnel. Since in basic research, a great number of tests has to be made, these desires are understandable.

The Twin-Screw Extruder ZK12P is available with a length of 24D or 36D.

The screws have a modular design and can be equipped with all common conveying, kneading and mixing elements. The cylinder elements have a length of 12D. Closed elements, degassing elements and side-feeding elements are available. The exact temperature control allows a working range of up to maximum 300°C. The maximum speed is 500min-1.

The machine is equipped with a touch screen control. The proven evaluation software FECON guarantees that all process parameters are recorded and that they are available for easy evaluation.

During the development of the machine, special attention was paid to quick and easy cleaning. With a few simple steps, the entire processing unit can completely be dismounted.

As part of a term paper at the Chair of Medical Technology at TU Munich and support from EVONIK, the machine was tested /10/. Here, poly (L-D, L)-lactide was mixed with hydroxyapatite.

The batch weight per test point was 100g. Throughputs of 250g/h to 710g/h were achieved. The time investment per test point was approx. 10min to 20min. However, the actual sample production took approx. 5min.
An important parameter for the mixing effect of a twin-screw is the specific energy introduced into the material via the screw. This also defines the basis for a scale-up of the process to larger machines. Therefore, also micro compounders are equipped with the evaluation of specific energy.

In /10/, the specific energy was directly compared with the mixing quality.

The pictures 17.1, 17.2 show impressively that this micro compounder does definitely fulfil the correlation between specific energy and mixing quality. Thus, the foundation stone for a scale-up to larger machine is laid. ■

# COMPLETE SOLUTIONS FOR DEVELOPMENT AND PRODUCTION

From the beginning, COLLIN Lab & Pilot Solutions is not a pure machine manufacturer but is strongly characterized by process engineering. This is also proven by the generously equipped technical centre, which takes up much space in the new company building. This circumstance and the well-trained and experienced personnel take comprehensively care of customer tests and together, complete solutions are found. Regular trainings make sure that the knowledge level of the staff is always up to date. The technical centre is not only used for tests during sales projects. In fact, it is open for everyone who is interested in tests. Furthermore, of course, all new developments of COLLIN Lab & Pilot Solutions are carefully tested and made ready for the market. Based on this company philosophy, over the years, a deep understanding for the final application of the products produced with their lines and thus for the necessity of challenging specifications has developed. ■

18.1

## Pelletizing lines

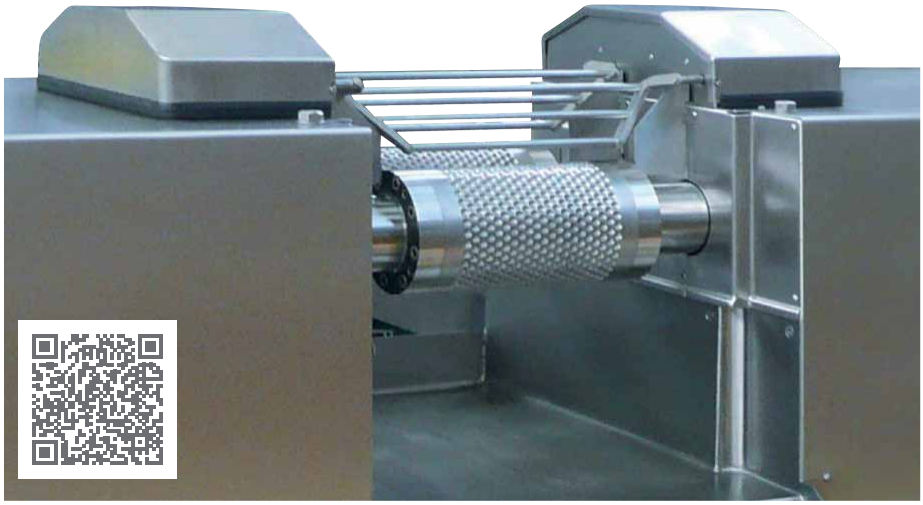
Normally, as downstream equipment of the compounder, cooling belts are used, since, generally, the use of water baths is only possible to a limited extent due to risk of contamination. A typical line configuration can be seen in the image 18.1.

In the GMP design, the cooling bath is made of stainless steel. The deflection rolls are water-cooled so that there is a permanent heat removal out of the belt. The controlled cooling belt speed in relation to the die outlet speed defines the strand diameter. The speed of the rotating cutting knives in the pelletizer defines the length of the pellets so that any desired dimension can be adjusted.

The picture 18.2 shows a second type. It is equipped with two additional vertically acting air knives. Thus, a higher cooling performance is achieved. However, it should be noted, if cleanroom conditions apply, increased effort regarding air filtration and air guidance may arise. Therefore, it is worth the economic view which type would be preferable. ■

18.2

# Continuous tableting



https://www.collin-solutions.com/en/product/calenders-roll-mills/ 19.1

According to the recipe, API, carrier material and other additives are fed into the compounder and there, they are continuously and smoothly mixed. Via a slot die, the final tablet mixture is directly discharged into the roll gap of a so-called shaping calender (see image 19.1). In the gap, a tape with the final tablet geometry is produced.

The tape is placed on a cooling belt and is guided into a „mill “where the final tablets are pressed out. The machine size is defined by roll diameter and working width. These sizes are available: Ø 202 X 400mm, ø202x200mm, ø110x200mm, ø120x60mm, ø60x20mm. The latter three sizes are designed for pilot productions and research.

The shaping calender is based on the highly precise measuring roll mill from COLLIN Lab & Pilot Solutions. It has all characteristics of this machine:

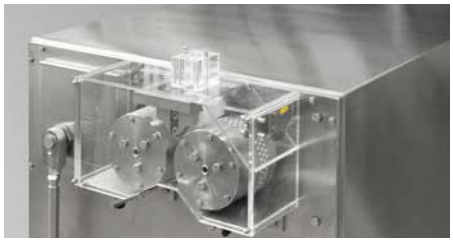
- Gap force up to 10t
- Automatic gap adjustment and control
- Gap force and torque measurement, as option: controlled version
- Precise drive, high true running accuracy and narrow gap tolerances guarantee exact and continuous tablet geometries
- A touch screen control records and documents all process parameters
- Fine-adjustment for an exact alignment of both rolls
- The rolls are tempered by liquid

The calender rolls are special. Each carries a half of the cavity of the tablet form, so that in the gap, the complete tablet is formed. For quick product change, also the design is essential. The shaping cylinders are each screwed between the separately mounted roll shafts. For mounting resp. dismounting, by motor, the rolls are moved into a position allowing easy access. Then, the screwings can easily and quickly be unscrewed resp. fixed. The shaping calender includes all mandatory safety devices.

In contrast to the production calenders (Ø202), the rolls of the smaller sizes are mounted on one side, which considerably speeds up the geometry change in research operation. This is very important because, among other things, the drug delivery heavily depends on the shape of the tablet.

Both images 19.2, 19.3 give an idea of these compact, flexible machines. For safety reasons, all housings are hermetically sealed.

19.2



19.3

The performance data is as follows:

- Roll diameter 120 mm
- Quickly exchangeable cavity sleeves
- Directly cooled cavity sleeves
- Speed range 0.3 min-1 to 13 min-1
- Hydraulic quick closing function of the gap
- Mechanical fine-adjustment of the gap: 0.08 mm to 3 mm
- Automatic gap measurement
- Maximum gap force 6500N »

- Manual height-adjustment of the processing unit, 150 mm
- Hydraulic quick opening of the gap to 30 mm
- The machine is completely sealed according to IP64
- Touch screen control
- For logical reasons, the smallest machine of the series is combined with a ZK12 (image 20.1).

The rolls of the calender are equipped with highly precise sleeves, which carry the cavity for the tablets. These sleeves can easily be exchanged. Thus, quick cleaning is guaranteed and different tablet shapes can be tested in a very early development phase. Moreover, this combination with smallest approaches quickly provides meaningful results in fundamental studies. ■

20.1

https://www.collin-solutions.com/en/product/strand-lines/

20.2

# Strand lines for API-loaded implants

The strand lines are designed for outer diameters of 6 mm and coextrusion of up to 5 layers. Also for these lines, the following principles apply:

- Compact design for minimal space requirement
- Quick dismounting and mounting of the components for quick and safe cleaning
- Minimal residence times for quick product changes
- Easy and safe handling by the operating personnel

In picture 20.2 of this chapter, a production line can be seen. The extruders discharge the materials into a multi-layer die, which has especially been calculated for this application. The spiral mandrel distributors of the die guarantee constant discharging speeds of the layers over the cross section. Due to the discharging accuracy, the extruders are followed by gear pumps. For the API-loaded layers, it is advisable to use compounders as direct extruders. From the economic and technical view, this is important, since, especially in case of thermally sensitive materials, an additional heating step is saved. The strand is vertically guided into the cooling bath, diverted at the deepest point and discharged again at the top. In front of the take-off, by laser, ovality and diameter are measured in two axes which are displaced by 90°. The diameter measurement is used for the take-off speed control. At the end, the strand is cut to the desired length.

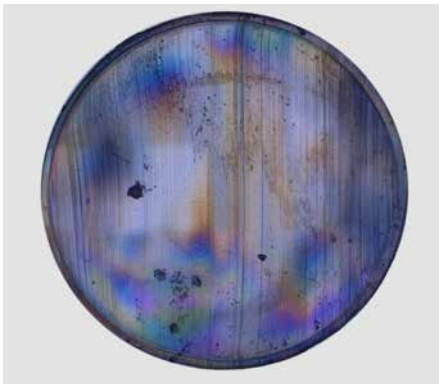
In the lower third, the cooling bath is pivot-mounted so that it can easily and laterally be pivoted out of the line for cleaning purposes. Via a heat exchanger and a water buffer tank, a constant water exchange provides the necessary heat removal. The water inlet is controlled in such a way that wave formation at the inlet of the bath is avoided and the water temperature has a constant level. The complete piping is made in stainless steel. Line speeds of up to 8m/min can be achieved. »

For product development and pilot production for pre-clinical studies and product approval procedures the development line shown in the picture 21.1 was manufactured.

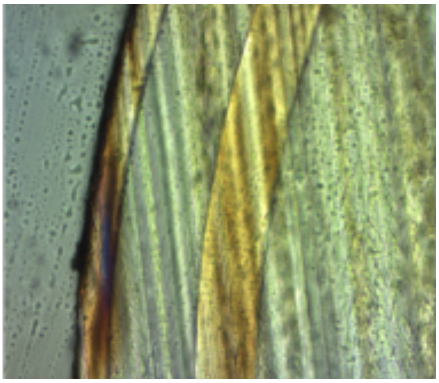
Essentially, it is different from a production line because the cooling bath is smaller. However, with 5m/min, strands in production quality are produced.

The quality of the strands, achieved with the technology from COLLIN Lab & Pilot Solutions, is impressively demonstrated by the three microtome sections. (pictures 21.2, 3, 4) ■

21.1



21.2



21.3

# Hose and profile lines

With line (image 21.5) speeds of up to 100 m/min, these lines are suitable for the production of the complete spectrum of hoses shown above. Normally, they are designed for 3-layer coextrusion. As option, also five and more layers are possible.

Further characteristics are:

- Diameter range outside: 0.5mm up to 4mm
- Ovality of <100µm guaranteed, <50µm achievable
- Automatic surface inspection
- Automatic sorting of faultless and faulty production
- With controlled vacuum and support air up to 5 Lumen
- In most of the cases support wire is not required ■

https://www.collin-solutions.com/en/product/tube-line-medical-line/

21.4

# Flat film lines

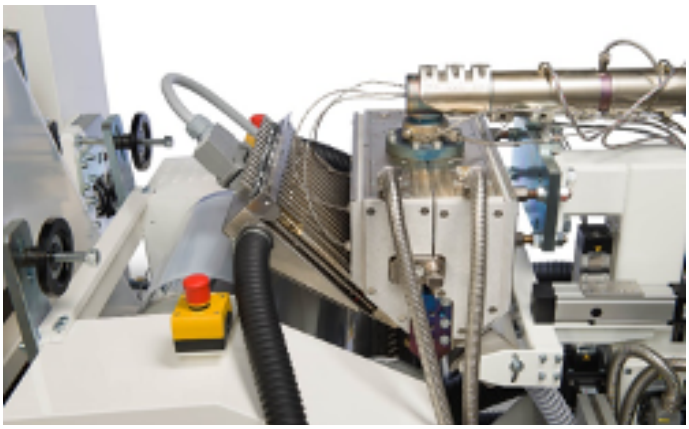
22.1

As example, one line of the variety of COLLIN Lab & Pilot Solutions lines, a cast line for the production of wound dressings is shown. The chill roll (CR) consists of two rolls with a diameter of 250mm and a working width of 400mm (further dimensions on request). The rolls are arranged in 45°. The die vertically feeds the first roll from above. The line is designed for 50m/min. Since in this case, a TPU with an adhesive tendency is processed, the rolls and all guiding rolls in the roller track have a non-stick coating. The range of thickness of the film is up to 650µm. The material selection for the components having direct contact with the product is according to GMP. The image 22.1 shows an overview of the entire line.

In order to achieve the narrow thickness tolerances after the starting within a short time and to keep them constant during production, a capacitive thickness measuring system is combined with a so-called automatic die, which is shown in detail (image 22.2).

At the appropriate point of the die, a thermo bolt will be assigned to the thickness measurement over the width. Depending on the deviation from the set value, the respective bolt is heated (die gap is minimized). In no time, the system achieves the tolerance range. It does not depend on the knowledge of the respective operator.

The film is wound in a double-station winder. Thus, bobbins can manually be changed during production speed. As option, embossing rolls are possible in order to specifically influence the surface structure of the film. ■



22.2

# Stretching of flat films

It has been known for a long time that the stretching of plastics essentially influences their characteristics. These include e. g. strength, chemical resistance, optical characteristics, haptics and breathability. A stretching procedure that is often used is monoaxial stretching in production direction (MDO). It is obvious that here, preferably a uniaxial formation of the film characteristics arises. In order to avoid that, the film will be biaxially stretched, i .e. in machine direction and transversely thereto. Continuous lines for this process require extremely complex drive and fixing systems for the film and therefore, they are very expensive. An economic alternative for development and production of small series is provided by the discontinuous stretching frame from COLLIN Lab & Pilot Solutions. The image 22.3 shows the machine manufactured according to ISO13485 with opened cover so that the real core – the stretching frame – can be seen. »

22.3

Into this, the film is manually be positioned by the operator. Behind the machine, there you can see the infrared panel for heating up the film to stretching temperature. The temperature measurement is made by infrared sensor, which is arranged in the heating panel in such a way that it is above the film surface in order to provide the actual value for the temperature control.

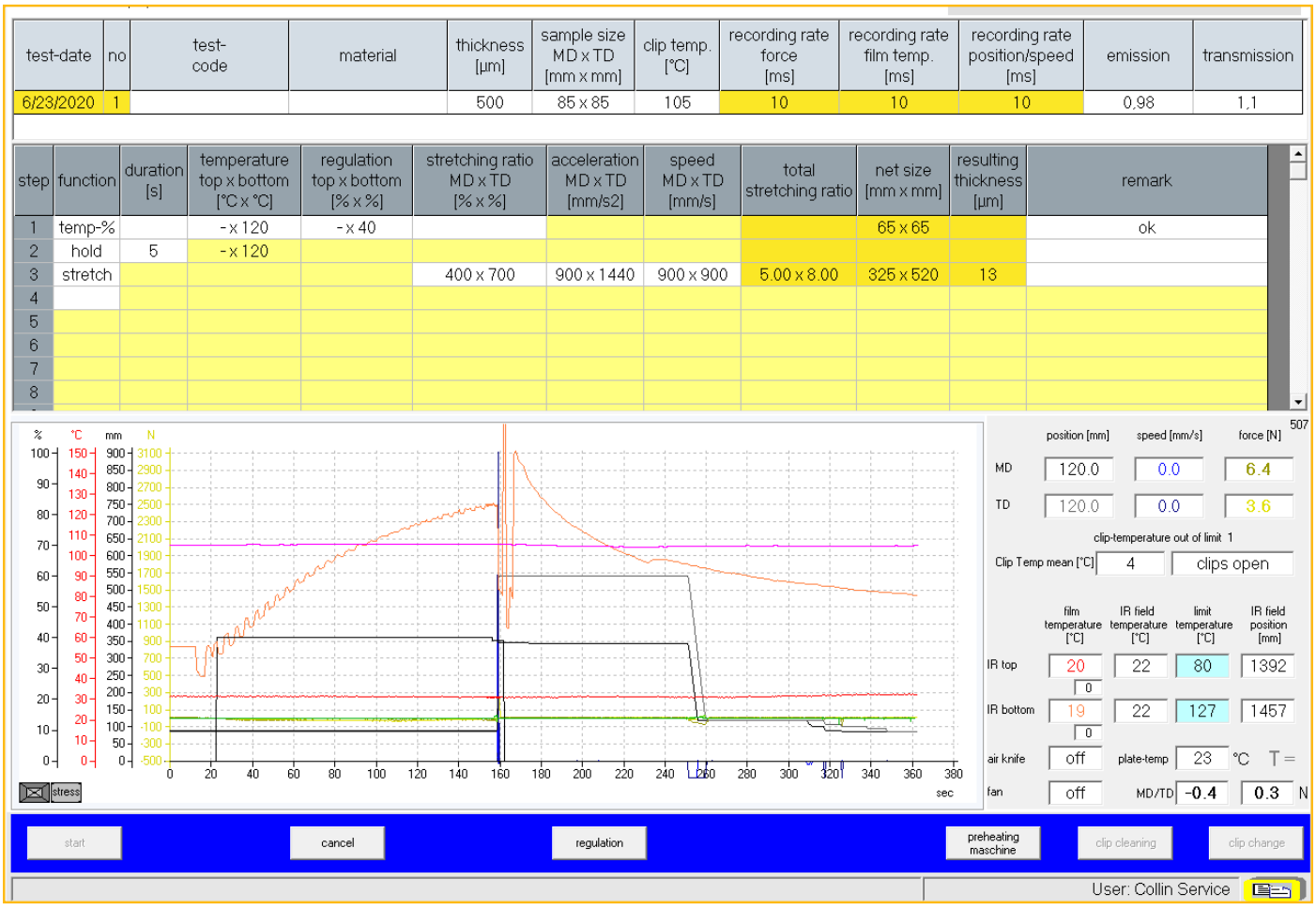
The stretching line includes the following main characteristics:

- Increased grip force in the clips (800N/clip) for stretching thick films
- Film heating by infrared radiation in order to achieve quick temperature changes
- Individually heated grip surfaces in the clips in order to achieve a better thermal homogeneity in the edge area of the film. Thus, the losses of film in the edge areas are minimized
- Self-explanatory, ergonomically designed machine control for quick training of the operating personnel
- Freely programmable test procedure with up to 32 automatically running process steps one after the other
- Complete documentation of all test parameters with easy operable evaluation software

The complete stretching process is entered into the sequence control system by the operator just one time. After the cover has been closed and after the run instruction, the complete stretching process automatically runs. The following image shows the main menu after the termination of a test. For a quick overview, the diagram includes the trend curves for:

- Film temperatures upper and / or lower side, light red and dark red
- Averaged clip temperature, purple
- Stretching forces in TD and MD direction, light yellow and dark yellow
- Travel distance of the stretching unit, black
- Forces for the mechanical protection of the machine, green

For every single stretching procedure, all administrative data as well as all process parameters are completely stored in an Excel program running in the background and thus, they are available for a comprehensive documentation and evaluation. ■



24.1

# Blown film for the packaging of medical liquids

For such a type of packaging, an essential requirement is the absolute transparency so that medical staff can visually check the content for any abnormalities immediately before starting the infusion. Furthermore, a certain elasticity, high puncture resistance and tensile strength must be guaranteed. For example, in case the bag falls to the ground accidentally, it will be avoided that it bursts. A certain weld strength is also necessary.

Originally, certain types of PVC were used. However, the discussion about the harmfulness of plasticizers, which has been continuing for years, resulted in the development of alternatives, especially in Europe. These are co-extruded films, whose outer layers include semi-crystalline polymers (e. g. PP) and the inner layer is made of elastomer materials.  In addition to the standard design of three layers, also considerably more layers with different material combinations can be realized.

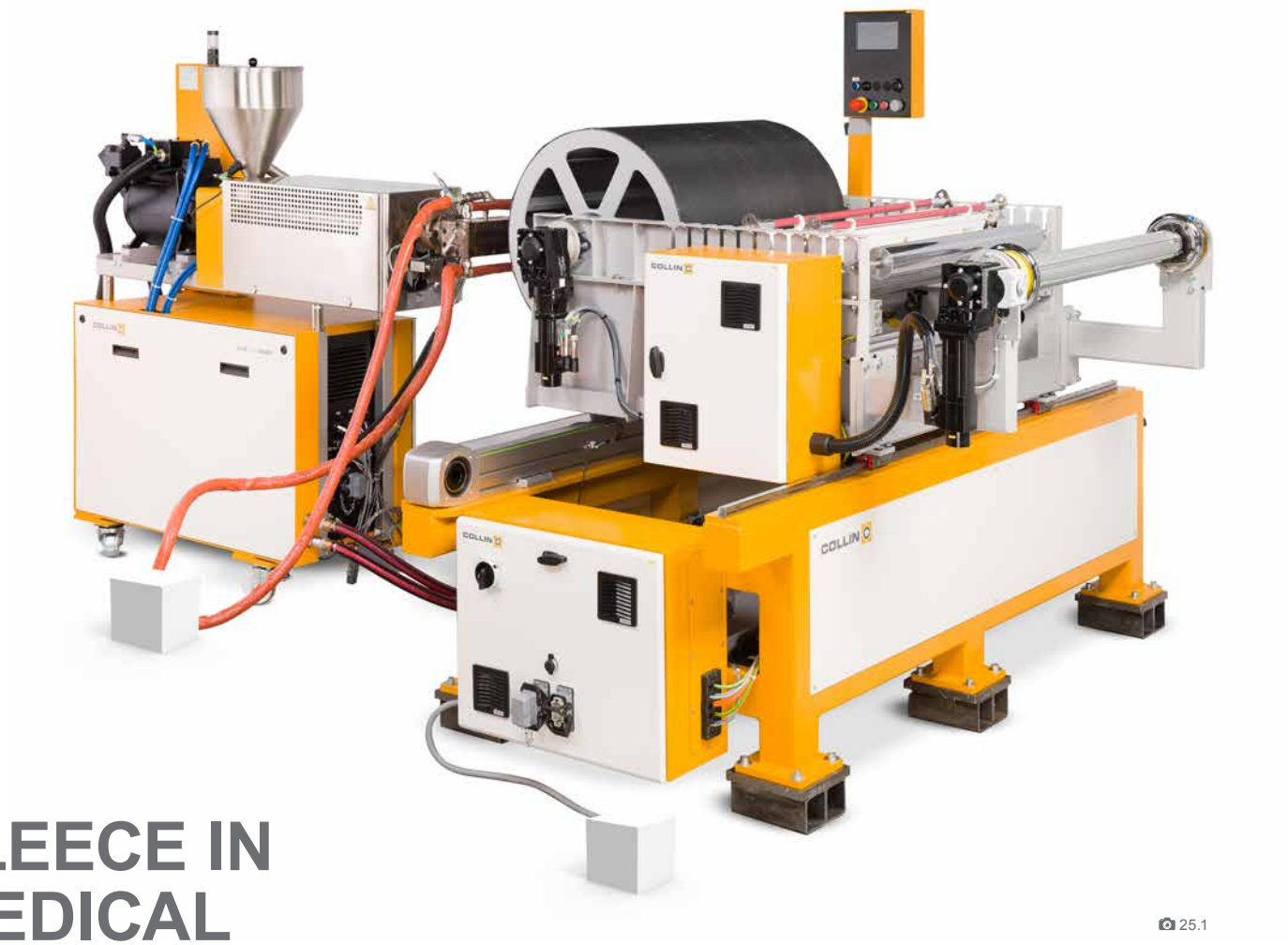
However, semi-crystalline plastics have the disadvantage that the formation of crystalline segments heavily reduce the transparency. The crystallinity essentially depends on the cooling speed (the quicker the more amorphous the more transparent). Standard blown film lines with air cooling do not achieve sudden cooling (quenching). For this purpose, an intensive water cooling is necessary. Therefore, the line concept is defined accordingly. The blown film is vertically guided into a water-cooled ring and there, it is suddenly cooled.

The first image 24.1 shows a compact quenching line from COLLIN Lab & Pilot Solutions. With this line, at smallest space requirement, a throughput of up to 30 kg/h can be run.

Performances up to 100kg/h can be produced with the second line (image 24.2). This is prepared for an extension to five-layer coextrusion operation. ■

https://www.collin-solutions.com/en/our-products/product-type/blown-film-lines/

24.2



25.1

# FLEECE IN MEDICAL TECHNOLOGY

Fleeces are used in a variety of designs for different filtering tasks. These include particle separation from the air, blood filtration, respirator masks etc. Particle sizes of >=5µm must reliably mechanically be separated. In order to avoid the permeability of viruses and bacteria, fleece is electrostatically charged.

As production process, the so-called melt blown process has been established for years. In very fine borings, the melt produced in the extruder, is formed in strands with a diameter of 250µm to 300µm. When exiting the die, these strands are caught by an airflow and thus stretched into fibres <=5µm and swirled at the same time. On a belt or a collector drum, they are cooled. The throughput of the die, the take-off speed and the transversal laying speed define the fleece structure, fibre density per surface unit and thickness.

Due to constant further development in this field, COLLIN Lab & Pilot Solutions has developed a line (image 25.1) for laboratory use and pilot production, which, however, is also suitable for small series production.

With it, with a vertical die, fleece widths of 600mm to 800mm with line speeds between 0.1m/min to 4,5m/min are produced. With a horizontal die, even up to 30m/min are achieved.

The collector has a diameter of 600mm and a width of 800mm. Spinnerets are available with a width of 200mm, 400mm, 600mm and 800mm. The number of holes can be up to 46 holes (0.25, 0.3mm). ■

Corné Verstraten
*CSO / Joint Partner COLLIN Lab & Pilot Solutions GmbH*


# COMMENT

## Focus on strengthening the establishment on the future market medical & pharma

The medical and pharma market – especially in Europe but also in Central America – remains as strong as ever. From the perspective of sales, we clearly recognize, that, at the moment, this sector is gaining momentum and the speed is increasing. Whether in case of inquiries, realisation or delivery times.

### Highest precision, homogenous processing & high throughput

Also the requirements on precision, tolerances, clean room conformity, flexibility of the lines as well as homogenous processing and throughput are increasing. Certified according to ISO 9001:2000, for nearly half a century, COLLIN has been manufacturing highly precise and compact extrusion lines for laboratory and pilot applications. Of course, this comprehensive expertise influences our medical solutions. The latter are built according to the guidelines of FDA 21 CFR, ISPE, ISO 13485, Din EN 10204/3.1B, cGMP/GMP and are explicitly adapted to the respective customer requirements.

### COLLIN high-end solutions & comprehensive spectrum

Our high-end extrusion lines with a speed of up to 120 m/min are omnipresent in medical technology and the pharma sector. The spectrum ranges from drug-loaded strands via the pelletizing of tablet pre-mixtures up to the mixing and dispersing of pigments. In the medical technology, customers use our high-performance compounders for example for the production of dental prosthesis or bone substitute made of PEEK.

### It is the aim to continue to accelerate the positioning on the market and to use potential

Although, we are already well-established on the market, in medical technology, we see great potential for our products. From the company turnover of about 27 million Euro, already now, we have gained a quarter in this sector.

With Thomas Nick as Sales Director Medical, we are perfectly prepared for the challenges on this strongly growing market and will accelerate the successful path we have already taken in the field of medical tubing as well as drug-loaded polymers.

Thomas Nick
*Sales Director Medical & Pharma*
*COLLIN Lab & Pilot Solutions GmbH*


With more than 25 years of experience in sales in plastic industry, Thomas Nick is the suitable contact person for customers in the medical technology and pharmaceutical sector. As Sales Director, he is responsible for the international sales of COLLIN extrusion solutions for this market segment.

Our product segment Medical Line includes the full range of medical extruders up to medical tube lines. Beside a variety of special roll mills for the pre-development and production of pharmaceuticals, we also develop and manufacture lines for the production of Infusion bags, medical sutures and wound dressings. The latest development is a production line for the production of medical face masks.

It is our aim to position COLLIN as partner of plastic processing companies on the international medical and pharmaceutical market even further and to accelerate the change in this sector significantly. ■

## Competence centre for extrusion dies

COMELT
COLLIN MELT SOLUTIONS

One of the COLLIN subsidiaries, COMELT GmbH, in the Upper Austrian Kremstal, the so-called plastic valley, pools the extrusion die competence of the whole group – from the development via the design and simulation by latest CFD software up to the manufacture.

Manufactured in Austria by 100%, the dies are the heart of every medical strand or tube line. For the market segment medical technology, which is so important to COLLIN, COMELT offers for example strand dies for drug-loaded strands, tube dies, filament dies or multi-filament dies. These are then used in laboratory operation as well as in production lines. ■

www.comelt.at

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Dr.-Ing. Franz Grajewski
*Chief Editor*

At the RWTH-Aachen, Franz Grajewski studied mechanical engineering with focus on energy technology. After that, he had been working as research assistant at the institute for plastic processing, RWTH Aachen for four years and was responsible for the working group rubber processing. He received his doctorate on process analysis and scale up at internal mixers for rubber processing.

After the doctorate, Grajewski had been working in different leading positions at Alcatel Kabelmetal for 11 years, mainly in the development of products and the production processes needed for the cable connection technology.

Then, he worked at Krauss Maffei Extrusionstechnik. There, he had the responsibility for the optimization and new development of lines as well as processes for pipe, sheet and profile production for 10 years.

From 2007 to 2019 Dr.-Ing. Franz Grajewski was responsible for process technology at COLLIN Lab & Pilot Solutions.

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