Brochure

Downstream tools shaping drug delivery

A practical guide to hot-melt extrusion and downstream tools shaping versatile dosage forms

thermo scientific

Hot-melt extrusion and downstream processing

Downstream processing is the bridge in pharmaceutical manufacturing between formulation and final dosage form. This guide explores how modern hot-melt extrusion (HME) workflows, combined with downstream tools from Thermo Fisher Scientific, enable the creation of solid oral dosage forms, films, implants, and personalized medicines—all with precise control over bioavailability, release profiles, and manufacturing efficiency.

The steps immediately downstream from HME are critical to achieving the desired properties of pharmaceutical products. Instruments that can shape, cut, or mold extruded material enable pharma developers to impart desired mechanical properties or create particular dosage forms.

Thermo Fisher Scientific offers modular downstream systems for extrusion setups, designed to help formulation teams move efficiently from R&D trials all the way to industrial-level manufacturing. These modular systems enable seamless progression from the early formulation research steps, where only small amounts of samples are being developed and tested, to a pilot scale with more practical amounts of product, and then to even larger production scale processes.

Downstream processing in pharmaceutical development

An extrusion process with a twin-screw feeder and twin-screw extruder guarantees a solid processing to gain good bioavailability and a good release profile in the drug development. However, the processing that extruded material undergoes upon exiting the extruder has major impacts on the utility and efficacy of the final product. For example, various solid oral dosage forms such as buccal tablets and transdermal patches, as well as new delivery systems like subcutaneous implants and transmucosal applications, can be produced using hot-melt extrusion—provided the extrudate is processed appropriately.

When the melted material exits the extruder, several downstream tools can be used to cool down the melt, solidify it, and shape it. Different dosage forms can be produced with the corresponding downstream equipment. Downstream modules might include a chill roll, which produces flakes that are very easy to mill, or perhaps a die with nozzle insert could be used in combination with a strand take-off, thus allowing a cylindrical filament to be formed and spooled.

The downstream process ideally should be considered as early in the R&D process as formulation development. During the continuous manufacturing workflow, specific product properties such as the elasticity or brittleness of the product require proper adjustments to the downstream process. Production concerns like throughput and efficiency are also dependent on the form selected. Importantly, factors such as bioavailability and release profile can be impacted by the way in which the extrudate is processed in the downstream stages.

Figure 1 includes an overview of different dosage forms that can be made with hot-melt extrusion and downstream processing, showing how versatile such a twin-screw extruder and downstream modules can be. Further details about how these various downstream processing tools work are explored in the following pages.

Figure 1. Dosage forms made possible via downstream processing of hot-melt extrusion.

Strand line and pelletization

A cylindrical strand is one of the most common forms imparted to an extrudate. Upon exiting the extruder, this strand line can be further processed into smaller pieces of different shapes and lengths, giving the manufacturer options regarding the final product. A pelletizer is a common downstream accessory, used to chop the strand into small pellets that may then be milled or compressed into other forms.

Strand line setup

In a strand line setup, an extruded strand is transported onto an air-cooled conveyor belt. It passes a permanent air stream that cools down the melt and solidifies the strand. At this point, the strand may be cut, but considerations do come into play when cutting an extruded strand: The strand must not be so brittle that it breaks when cooled strand is pulled off to be cut. At the same time, a strand that is too elastic is inappropriate since such strands tend to jump or pop out of the pelletizer. Appropriate behavior of the strand is necessary for effective drug development and preparation.

Varicut pelletizer

The Thermo Scientific™ Varicut Pelletizer, which is designed like a rotating knife and cuts the strand into cylindrical pellets of 1 to 3 mm in length, is typically located at the end of the conveyor belt. The final pellet size is determined by the pace of the conveyor belt as well as the speed of the of the Varicut pelletizer blades. The speed of the conveyor belt is dependent on the extruder line speed.

Face cut pelletizer and direct die-mounted cutting

A face cut pelletizer may be implemented to generate regular shaped pellets of the size 0.5 to 2 mm. In comparison to the Varicut pelletizer this downstream equipment is directly mounted to the die of the extruder. The cutting knife is located immediately adjacent to the die and homogeneous pellets are achieved (see Figure 2). In this case, the cooling of the extrudate is not necessary, although when using a face cut pelletizer it is strongly recommended to have a highly filled, non-sticky product with 20–50% solid content in melt. This allows shear stabilization, which enables the material to be cut off easily.

Pellet size, milling, and downstream handling

Small pellets are advantageous for easy milling. This is relevant for capsule filling or compressing powders with a tablet press. Higher throughput of small pellets can be achieved if there are multiple outlets in the die, as the blades could cut through multiple strands simultaneously.

After cutting, pellets are usually guided into a cyclone where they can be shaped to have rounded ends or edges. While cylindrical pellets are obtained from the Varicut pelletizer, the face cut and cyclone process generates pellets that are more rounded.

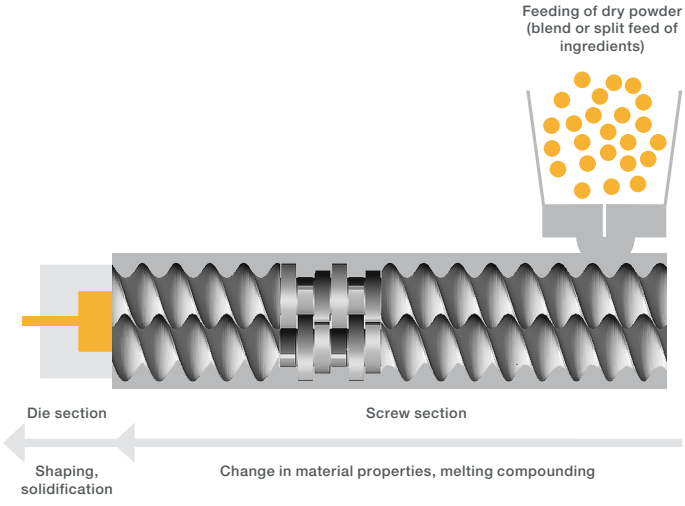


Figure 2. Schematic of face cut pelletization.

Chill roll processing and sheet take-off

While strand and face-cut pelletizers are ideal for producing granules and pellets for capsule filling, chill-roll lines offer greater control and improve on factors like brittleness and elasticity for milling applications.

Chill roll processing

The chill roll is a type of temperature-controlled conveyor system that is generally applied in a higher throughput manufacturing setup. It also helps to simplify milling in later steps. With a chill roll, the melt flows out of the extruder die onto two cooled rollers with a defined gap and rotational speed. The cooling rate of the rolls is regulated with a thermostatic bath. The rolls counterrotate, drawing the material into the gap, simultaneously forming a thin film and cooling it down. The film is then conveyed against a scraping blade to peel off a sheet (see Figure 3).

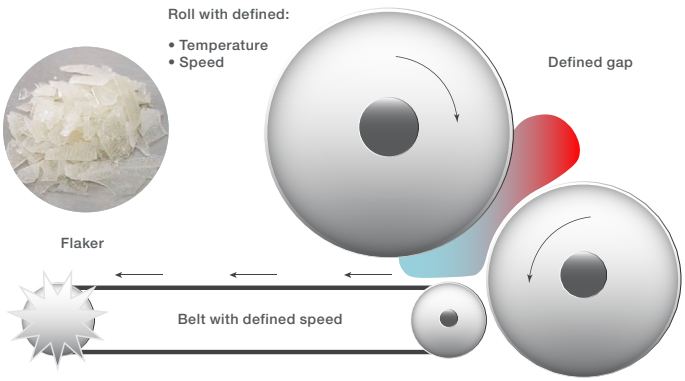


Figure 3. Schematic drawing of the flake processing with the chill roll.

This sheet is conveyed along the chill roll conveyor belt at a defined speed and at the same time it is further cooled before it is crushed into irregular shaped flakes by the rotating flaker. The flake size can be varied either by adjusting the gap size between the rolls or by changing the rotational speed of the flaker.

Sheet take-off

A suitable sheet die followed by a sheet take-off is utilized for film production, especially for the oral dispersible films application (see Figure 4). Orally dispersible films (ODF) for instant drug delivery through the buccal cavity are typically made by a film casting process. But ODF can also be made by HME, overcoming all issues with processing of solvents. Depending on the die slit size it is possible to obtain sheets with up to 30–800 µm sheet thickness. The sheet undergoes wind-off onto a spool and later gets cut into the required sheet size(s). Choosing the aforementioned sheet-die and an appropriate formulation this setup can also be used to produce adhesive patches. An adhesive patch is placed on the skin to deliver specific dose of API which is absorbed through the skin into the bloodstream in controlled release. HME can benefit for different patch types e.g. single layer patches where drug and adhesive are mixed together and extrudes as a strand that is applied onto a carrier film.

Benefits for brittle or elastic materials

The most important advantage of the chill roll is the well-controlled and well-defined cooling which is beneficial and necessary to have an amorphous dispersion. The morphology of the extrudates is controlled in a continuous and reproducible process. Furthermore, the chill roll is suitable for various types of materials. It is especially beneficial when working with brittle materials that are hard to handle, high- and low-viscosity materials, as well as elastic materials. Many pharmaceutical polymers are quite brittle. In contrast, extruded thin sheet films in which an API has been incorporated are often elastic and stretchable, and feature a quick dissolution in water on the order of a few seconds. The API is either dissolved or suspended as crystals or amorphous particles in the polymer matrix of the film.

In total, the chill roll setup is compact with a small footprint. Recent studies show that a chill roll's production of flakes that are very easy to mill is clearly superior to pelletization of the extrudate.

Figure 4. Setup for ODF manufacturing. From right to left: (a) Thermo Scientific™ Pharma 11 Twin-Screw Extruder; (b) sheet die; and (c) Thermo Scientific™ Pharma Sheet Take-Off.

Filament production and 3D printing

Extrusion dies and downstream accessories can be swapped out to allow for production of different shapes and sizes of products. Chill rolls, as discussed above, are excellent for making thin films for patches or the like. Filaments, on the other hand, can be used as precursors to other dosage forms.

Strand take-off

The creation of different and unique extrudate shapes is made possible by varying the die design. For example, if a die with nozzle insert is used in combination with a strand take-off, a cylindrical filament can be formed and spooled. This filament could then be used for the 3D printing of personalized medicine (see Figure 5). For example, for patients who need a dose that is not commercially available, a physician can prescribe a specific, customized dose. This allows for precise tailoring of medication based on a patient's age, weight, or metabolic profile, which is particularly useful for pediatric and geriatric patients. Another possibility would be the 3D printing of a multi-drug combination in single tablet that combines multiple active pharmaceutical ingredients (APIs) and different release profiles. This reduces the number of pills a patient must take.

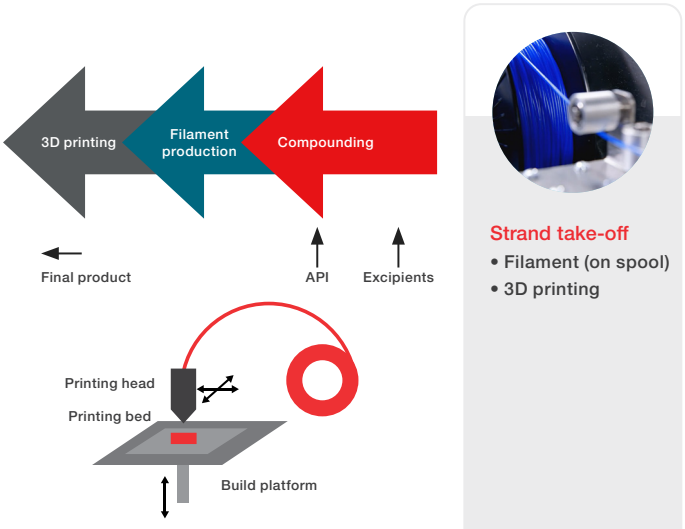


Figure 5. Schematic of 3D-printing filament production for personalized medicine.

Any 3D printing precision will be dependent on the consistency of the filament diameter; obviously, a strand that varies in thickness will not be capable of forming regular, consistent structures. When monitoring the diameter of the strand, a laser gauge can be used. A laser gauge is a non-contact measurement system used to continuously monitor and control the diameter, ovality, and other dimensions of extruded products. Implementation of a laser gauge can help to guarantee the uniformity of the extrudate.

Using extruded strands for 3D printing allows for the creation of novel drug delivery forms with modified release profiles. Depending on how the HME process is used to disperse the API withing the extruded filament, the rate at which a drug is released in the body can be controlled. This engenders options for immediate, sustained, delayed, or pulsatile release, which is critical for time-sensitive therapies where drugs need to be released at specific times of the day.

Injection molding, implants, and co-extrusion

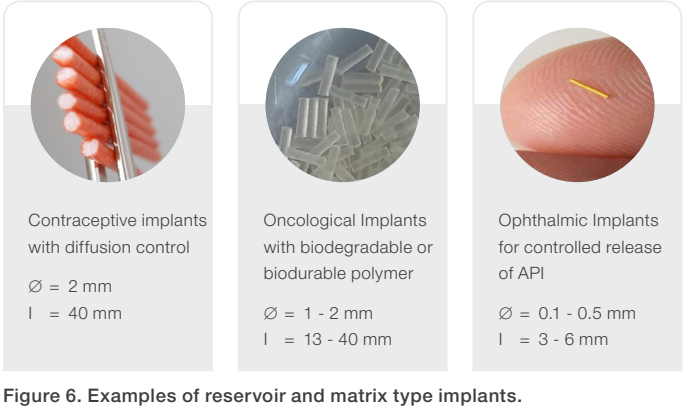
Another technique for downstream processing that can lead to distinct advantages in pharmaceutical processing is injection molding. When an injection mold is used with extrudate under high pressure, customized shapes can be formed within small tolerances, and these in turn can be used to enhance drug delivery in forms like implants.

Injection molding

Injection molding is applied for the production of single specimens for mechanical testing or tablets for bioavailability and dissolution studies. Further process steps such as milling or tableting are not necessary. Injection molding equipment allows unique shape formation (e.g., sheets, capsules, tablets, etc.) at a high process pressure. The shapes are very reproducible and have a high homogeneity in weight and shape. This process is very fast and cost effective, especially when producing large quantities. A specimen can be produced from different materials—from melt, pellets, or powders. Compared to the above-listed downstream equipment, the final product from injection molding has a high density which is not suitable for fast release or high dissolution products. The application is more suited for sustained drug release and is interesting for implants.

Subcutaneous implants

Alternative drug delivery methods such as injectable implants (e.g., oncological or ophthalmic implants; see Figure 6) and vaginal rings for transmucosal drug delivery are gaining more and more importance. Biodegradability (the implant dissolution over time), as well as biocompatibility (the implant extraction from the body after time), are compatible with hot-melt extrusion. Hot-melt extrusion not only compounds the ingredients, it also directly shapes the specimen within small tolerances. In addition, reservoir type products surrounded by a polymer membrane can be co-extruded and different, more controlled release rates can be obtained (see Figure 7).



Contraceptive implants with diffusion control

∅ = 2 mm
l = 40 mm

Oncological Implants with biodegradable or biodurable polymer

∅ = 1 - 2 mm
l = 13 - 40 mm

Ophthalmic Implants for controlled release of API

∅ = 0.1 - 0.5 mm
l = 3 - 6 mm

Figure 6. Examples of reservoir and matrix type implants.

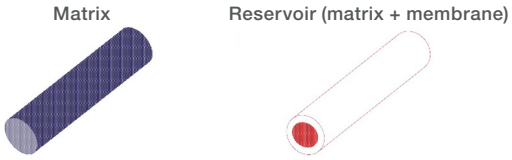


Figure 7. Schematic of a matrix and of a reservoir implant for a controlled release rate.

Co-extrusion

A co-extrusion setup is needed for specific tasks like manufacturing contraceptive implants. The inner core, (e.g., the API-polymer mixture) is extruded at a higher throughput compared to the membrane (e.g., polymer only, depending on the formulation). An example of this is shown in Figure 8.

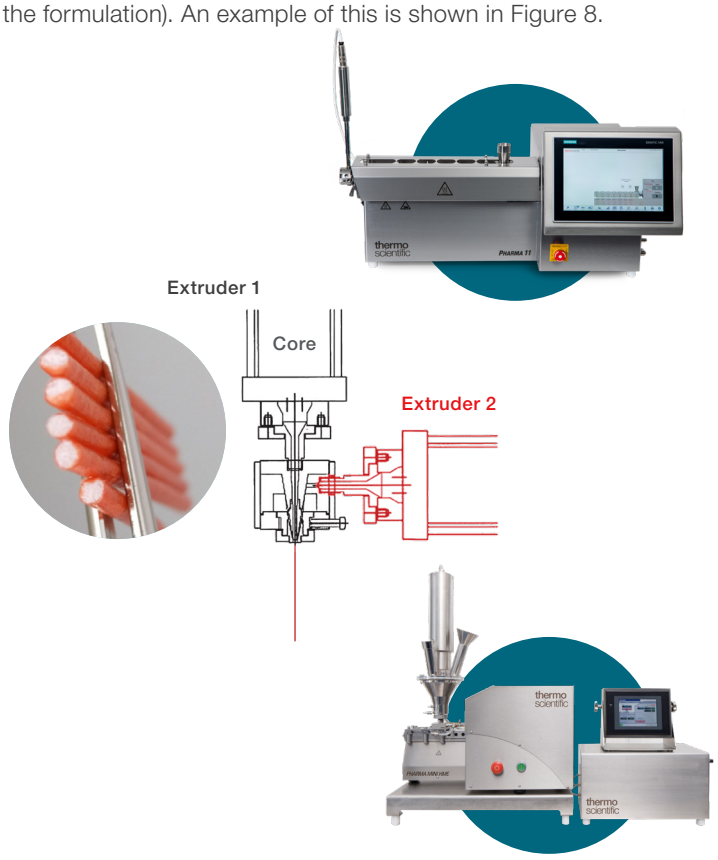


Figure 8. Co-extrusion setup with Pharma 11 Twin-Screw Extruder for core extrusion and Thermo Scientific™ Pharma *mini* HME Micro Compounder,r for membrane extrusion.

The co-extrusion setup includes core extrusion as done by a parallel twin-screw extruder, along with a conical twin-screw extruder for the membrane extrusion. Each extruder has its own feeding system. The throughputs must be selected properly, taking into account the final implant size as well as membrane thickness. For the co-extrusion process, it is essential to check the throughputs of both the core and the membrane to obtain the desired membrane thickness and implant design. The density of the core material as well as the membrane thickness are needed to calculate the cross-section area of the combined core-plus-membrane and determine the total volume flow. The melt flows of both extruders are combined with a co-extrusion die into a co-extruded strand. The manufacturing of implants can be performed manually and/or continuously. With a standalone compounder and a calibrated take-off/cutting device, implants can be pulled into the desired implant diameter (see Figure 9). A one-axis laser gauging measurement is applied for precise diameter determination, and the conveying belt speed is controlled based on this measurement. Precise and flexible cutting is provided by different cutting chambers. For implant cutting, a rotary cutter can be assembled with up to 4 blades, or a linear cutter can be used for more brittle materials.

Figure 9. Standalone compounder and calibrated take-off / cutting device.

Summary

The many downstream processing accessories available for use with twin-screw extruders give rise to a world of possibilities in pharmaceutical production. From chill rolls and sheet take-offs to strand dies, pelletizers, and injection molds, modern pharmaceutical manufacturing has a wealth of options for the production of novel forms of drug delivery. Continuous manufacturing through hot-melt extrusion and a variety of downstream processing tools helps make the connection between formulations and final dosage forms. These downstream processes transform molten extrudate into finished, application-ready dosage forms—enabling greater formulation flexibility, reliable scalability, and more efficient development.

Here is a recap of downstream processing accessories to HME and the dosage forms they help produce:

Dosage form	Typical downstream setup	Key advantage
• Pellets / granules	• Strand line or pelletizer	• Uniform particle size for capsule filling
• Films / sheets	• Chill roll	• Enhanced cooling and controlled solidification
• Tablets	• Pelletizing + milling	• Consistent particle size distribution
• Implants / controlled-release forms	• Die face cutter	• Precision shaping and morphology control
• Custom implants / sustained release	• Injection mold	• Unique shapes, high homogeneity

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