

Chapter 2

Twin Screw Extrusion for Pharmaceutical Processes

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Abstract The use of twin screw extruders (TSEs) to create sophisticated dosage forms is expanding because the continuous melt extrusion (ME) process has been proven to be a consistent and repeatable way to make high-quality products. TSEs are continuous small mass continuous mixers that are the plastics industry's preferred manufacturing methodology for compounding and devolatilization. It is without question that pharmaceutical companies have reaped the benefit of over half a century of technological developments and process refinement in plastics. It is only in the last decade or so that extrusion has emerged as a viable platform for pharmaceutical development.

This chapter will describe the design and functionality of co-rotating and counter-rotating TSEs for pharmaceutical applications. Screw and process design to facilitate effective mixing are addressed. Control parameters and the associated interactions (i.e., screw rpm versus feed rate) to achieve a quality product are proffered. Common TSE terms are defined and examples of useful TSE formulas are presented and explained. Staging of unit operations in a TSE and downstream system functionalities are described. Case studies are also presented to provide insight into how melt extrusion is being applied today. Finally, potential future growth areas are identified for melt extrusion.

2.1 Introduction

The use of twin screw extruders (TSEs) to create sophisticated dosage forms is expanding because the continuous melt extrusion (ME) process has been proven to be a consistent and repeatable way to make high-quality products. TSEs are continuous small mass mixers that are the plastics industry's preferred manufacturing methodology for compounding and devolatilization. It is without question that pharmaceutical companies have reaped the benefit of over half a century of technological developments and process refinement in plastics. It is only in the last decade or so that extrusion has emerged as a viable platform for pharmaceutical development.

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Fig. 2.1 Twin screw extruder with feeders for processing pharmaceuticals



Driven by FDA's Process Analytical Technology (PAT) initiative, the use of TSEs has been embraced by virtually every major pharmaceutical company. The PAT initiative encourages that new dosage forms be manufactured via continuous processes with in-line monitoring of key parameters—it literally could have been written by an extruder supplier.

TSEs for pharmaceutical class installations, as compared to most plastics installations, must also integrate validation documentation into the scope of delivery. Detailed/project specific document packages for the Factory Acceptance Test (FAT), Installation Qualification (IQ) and Operational Qualification (OQ) add months of time and effort to the installation and commissioning of the equipment. There are also cGMP guidelines for cleaning pharmaceutical class TSE systems. For instance, the equipment must be cleaned at appropriate intervals and written procedures are required that must be specific and detailed. Cleaned equipment must be protected from contamination while in storage and inspected just before using. Records and equipment logs of all cleaning and inspection must be kept, and the time between end of processing and cleaning steps must be recorded (Martin 2012a).

The goal of this chapter is to provide insight into the design of TSEs, and how these devices are and can be applied to manufacture novel dosage forms in a precise and economical manner (Fig. 2.1). Some simple formulas are interspersed within the text to provide insight into the TSE design and process.

2.2 TSE Design and Applications

Let us start with some simple definitional terms. In a TSE there are, obviously, two screws that fit inside a “figure eight” barrel. The outside diameter of each screw is referred to as the OD, and there is an overflight gap between the tip of the screw and

Fig. 2.2 TSE terms: OD, ID, and overflight gap

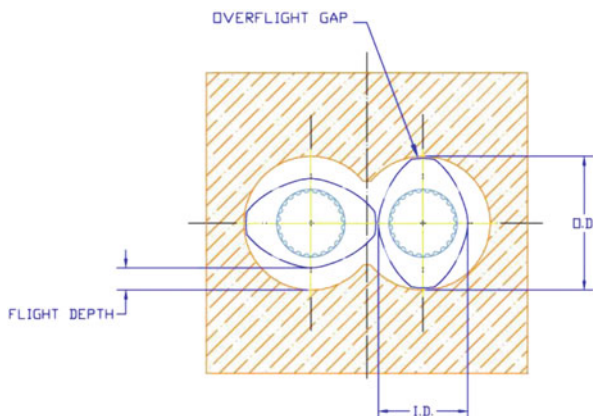
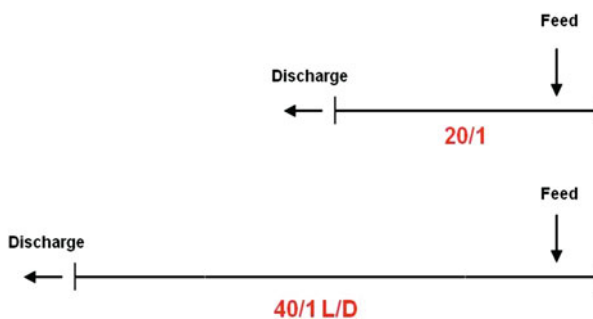


Fig. 2.3 Comparison between 20/1 and 40/1 L/D TSE process section lengths



the barrel wall. There is also an inside diameter (ID) of each screw. In a TSE, the OD and ID are constant throughout the length of screws. OD divided by the ID gives you the OD/ID ratio, which determines the flight depth and the free volume in the process section. See Fig. 2.2 for a schematic that defines some typical TSE terms.

The length of the barrel process section is frequently described in terms of the length to diameter (L/D) ratio, with greater L/D values indicating a longer process section. The L/D ratio is defined by dividing the overall length of the process section by the diameter of the screws. For most pharmaceutical compounding operations L/D values ≤ 40 are used, while reactive and devolatilization extrusion operations may utilize longer, such as 60/1 L/D process sections. Heat- and shear-sensitive products often use shorter process sections, such as a 20/1 L/D process length. It becomes obvious that the longer the L/D the more unit operations can be performed along the length of the process section.

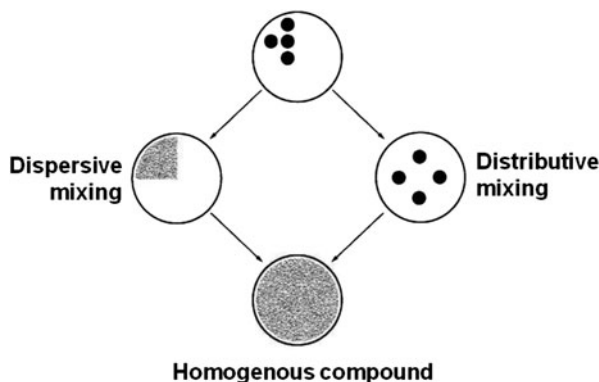
For instance, if the OD of a screw is 20 mm and the length of the process section is 800 mm then the L/D ratio is 800/20 or 40/1. If the length was 400 mm the L/D would be 400/20 or 20/1 (Fig. 2.3).

TSEs perform dispersive and distributive mixing. The intense mixing associated with the short inter-screw mass transfer distances inherent with a TSE results in highly efficient mixing and a more uniform product as compared to large-mass batch



Fig. 2.4 TSE co-rotating intermeshing screw set

Fig. 2.5 Dispersive and distributive mixing comparison



mixers with much longer mass transfer distances. The short residence time associated with a TSE (typically less than 2 min and as short as 5 s) is particularly beneficial for heat/shear-sensitive formulations, as the TSE can be designed to limit exposure to elevated temperatures to just a few seconds (Fig. 2.4).

In dispersive mixing, agglomerates or liquid droplets held together by interfacial tension are subjected to mechanical stress by the rotating screws to achieve size reduction. The most important flow characteristics to achieve dispersive mixing are the extensional and planar flow fields as generated by TSE mixing elements. In distributive mixing, repeated rearrangement of the minor components without size reduction enhances product homogeneity (Fig. 2.5).

The modular nature of TSEs offers process flexibility with regard to screw design, barrel configuration, and shear intensity. The co-rotating intermeshing TSE mode dominates the market, having captured approximately 90 % of current installations. Co-rotating intermeshing TSEs are very efficient at feeding powders and for staging of downstream unit operations. Counterrotating TSEs are also utilized in the pharmaceutical industry and have shown great promise in many applications. For instance, counterrotating intermeshing TSEs can be designed so that the materials being processed experience a tighter residence time distribution, and can provide more efficient pumping into a die (Martin 2001; Fig. 2.6).

In the plastics and food industries, TSE screw diameters (ODs) range from 5–400+ mm with outputs from a 20 gm to 50,000+ kg/h. Pharmaceutical TSEs are generally 60 mm and below, due to more efficient heat transfer characteristics of smaller extruders and, of course, the smaller batch sizes associated with pharmaceutical as compared to plastic products. Research and development efforts for pharmaceuticals are generally performed on TSEs with screw diameters in the 10–30 mm range.

The TSE utilizes a modular design for barrels and screws (Fig. 2.7). Segmented screws convey and shear the materials in channels bounded by screw flights and barrel

Fig. 2.6 Co-rotating and counterrotating intermeshing TSE geometries

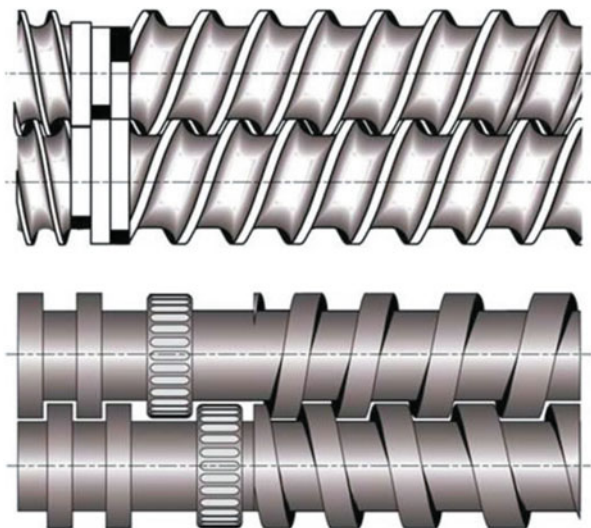


Fig. 2.7 Modular TSE process section



walls, with short mass transfer distances. Solids conveying and melting occurs in the early stages of the process section followed by mixing and devolatilization. Discharge elements then build and stabilize pressure prior to exiting the extruder.

The controlled pumping and wiping characteristics of the TSE screws in combination with a segmented design allows specific screw element geometries to be matched to the unit operations being performed in the TSE process section (Fig. 2.8).

TSE control parameters include screw speed (rpm), feed rate, process temperatures, and vacuum level. Melt pressure, melt temperature, motor amperage, and various in-line sensors also monitor the process to ensure a consistent/quality product. State-of-the-art extruders utilize programmable logic controllers (PLCs) for logic functionality that implements graphical touch-screens, data acquisition, and recipe management as standard features. It is also now routine to integrate sub-system PLCs with a supervisory PLC for integration of complex equipment from multiple suppliers, referred to as “distributed processing” (Fig. 2.9).

Co-rotating TSE design

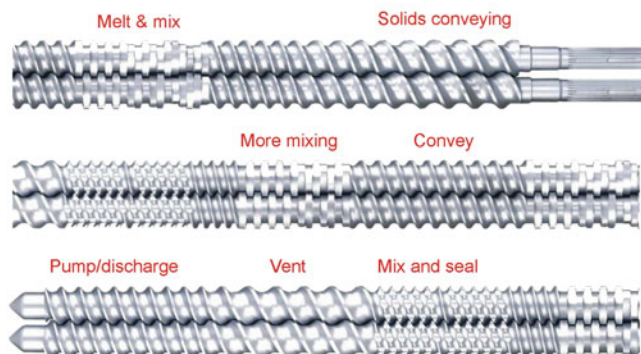


Fig. 2.8 TSE segment screw set with unit operations denoted

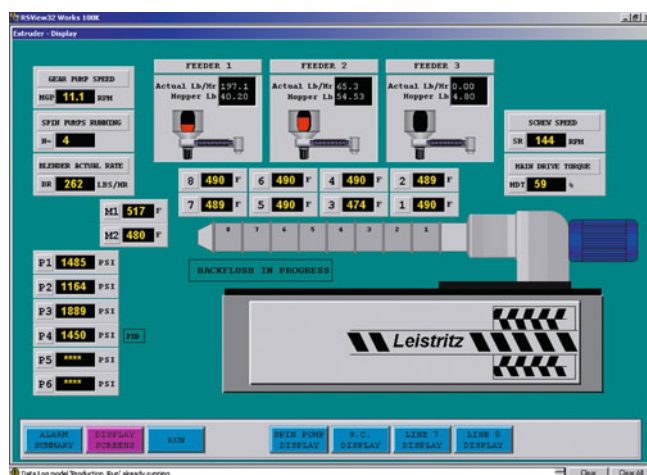


Fig. 2.9 Human Machine Interface (HMI) touch screen

Pharmaceutical class TSEs generally adhere to FDA part 11 of Title 21 of the Code of Federal Regulations, which defines the criteria under which electronic records are deemed trustworthy. Practically speaking, this regulation requires drug makers to implement controls, audits, and system validation for software and systems involved in processing electronic data. Protocols must be followed with regard to limiting system access to authorized individuals, operational checks, device checks, controls over systems documentation, and a plethora of other guidelines. Strict adherence with regard to copies of records and record retention is part of the guideline (Kapp and Palmer 2003).

Starve feeding refers to when the extruder is fed at a rate less than the forwarding efficiency of the screws. TSEs are almost always starve-fed, with the output rate determined by the feeder(s). The TSE screw rpm is independent and used in concert

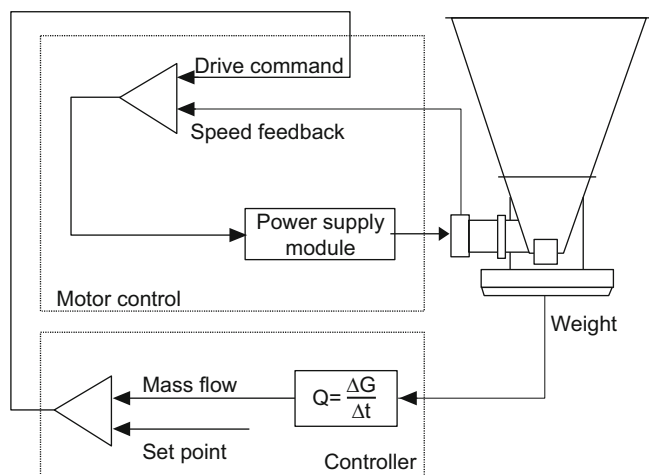


Fig. 2.10 Loss-in-weight feeder control functionality

with the feed rate to optimize compounding efficiencies. Feed rate versus screw rpm, and screw design, impact the average residence time (RT) and residence time distribution (RTD) for the materials being processed. Typical RTs are in the 15 s–3 min range (Martin 2001).

Feeders also maintain formulation consistency and are situated at different locations along the TSE process section to introduce ingredients in the proper order. The accuracy of the feeding system is critical to maintain uniform product quality. For this reason, loss-in-weight (LIW) feeders are normally specified to ensure that the ingredients are delivered at a constant mass flow rate to the extruder (Fig. 2.10). LIW feeders can meter either a premix or individual components to the TSE, as dictated by the formulation and desired level of continuous processing/monitoring. Volumetrically controlled feeders for solids are generally only used with a premix or at very low rates (i.e., 20 g/h), where LIW controls become impractical.

A LIW feeding device consists of the feeding module, the feeder hopper, a refill device, a load cell, and a control system. In an LIW feeder, the mass flow rate is calculated by dividing the weight reduction in the hopper by the time interval. At short/determined time intervals, the weight is measured and transmitted to the controller. The real-time mass flow rate is calculated from the weight reduction per unit time. To compensate for the difference between the set point and the measured value of mass flow, the motor speed is continuously modified. In operation, the feeder, hopper, and material are continuously weighed, and the feeder's discharge rate (which is the rate at which the feeding system is losing weight) is controlled to match the desired feed rate. With this technology, a constant mass flow to the TSE is ensured and verified.

The LIW principle is also utilized for the delivery of the liquids to the TSE. There are a variety of different types of pumps that may be specified based on the viscosity range and changeover requirements for the liquid being introduced (piston pump, gear pump, peristaltic pump, among others). Liquid injection systems can be

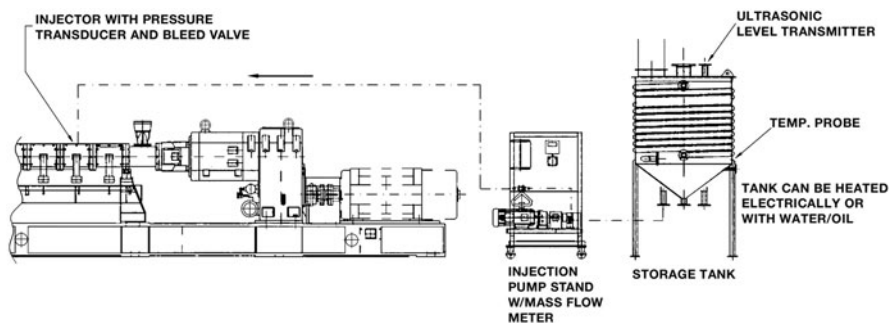
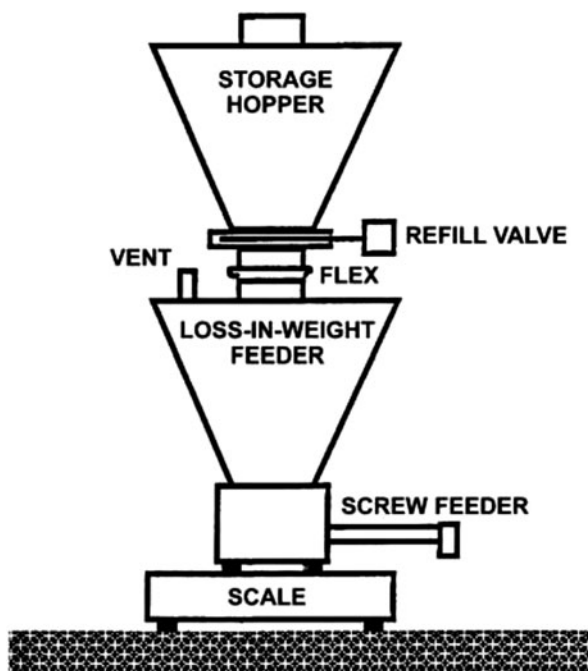


Fig. 2.11 Example of heated liquid feed stream to a TSE

Fig. 2.12 Refill system connected to LIW feeder



supplied as ambient or heated. The mass flow rate is measured and controlled by a liquid tank placed on load cells with the same LIW control to control the pump motor speed. Alternatively, a mass flow meter can be used to control and monitor the fluid rate to the extruder (Fig. 2.11).

Refilling a LIW feeder is an important part of optimizing feeder technology. In the refill mode, the LIW feeder must maintain a constant flow of material to the TSE. Refill times should be relatively short to allow the feeder to return to a true LIW operation. Additionally, the flow cutoff action to the LIW feeder must be quick and sure. Options include slide gates, flap valves, modulating butterfly valves, and rotary valves. Butterfly valves are often specified due to their easy-to-clean design and utility in a high containment environment (Martin and Nowak 2011; Fig. 2.12).

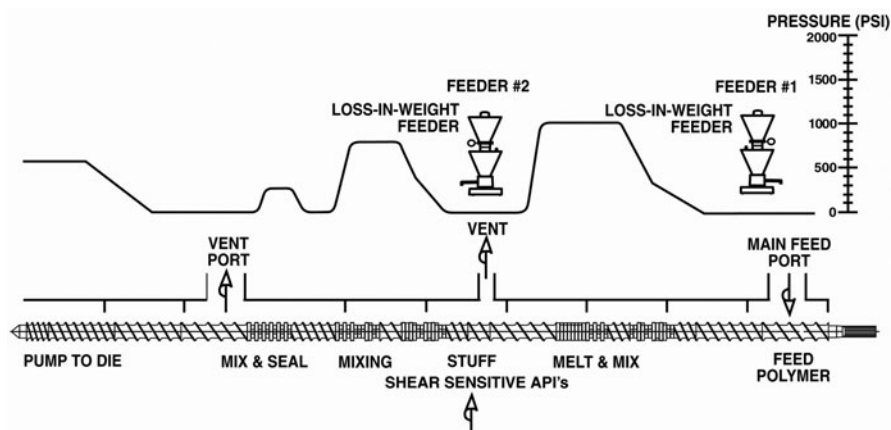


Fig. 2.13 Controlled pressure profile in starve-fed TSE

The pressure gradient in a TSE process section is determined by the selection of screws. Flighted elements are strategically placed so that the screw channels are not entirely filled, which results in zero pressure underneath downstream vent/feed sections. The controlled pressure gradient allows entrapped air, moisture, and other volatiles to be efficiently removed by vents without vent flooding. The zero pressure locations also facilitate the downstream introduction of heat and shear-sensitive active pharmaceutical ingredients (APIs) late in the process section to minimize exposure to shear forces and dwell time in the melt stream (Fig. 2.13).

A “side stuffer” is a device that is often used in a TSE system to introduce shear-sensitive APIs into the process melt stream. A side stuffer utilizes co-rotating, intermeshing, self-wiping screws that “push” materials into an unfilled section of the TSE screws. The side stuffer barrel is jacketed for liquid cooling/heating. Side stuffing is desirable for processing a high percentage of API into the process to facilitate more efficient melting/wetting/mixing by avoiding the plastication zone. A side stuffer is also starve-fed and requires its own LIW metering feeder upstream to set the rate (Martin 2001; Fig. 2.14).

The TSE and related devices are often placed within a process containment isolator when handling high-potency APIs. Sometimes just the API feed system is contained in an isolator unit. Door panels utilize gaskets with compression latches and connections are hermetically sealed. View panels are fitted with glove ports that are sealed, and primary chambers are configured with HEPA-filtered exhaust. As TSE systems are custom designed, isolator systems are built-to-order based on the occupational exposure level (OEL) of the installation, as well as TSE system features, the range of products, and batch size (Fig. 2.15).

The gearbox of a TSE transmits energy from the motor to the screws, and reduces the motor speed to the desired screw rpm while multiplying torque. TSEs typically utilize various failsafes to prevent gearbox damage in an over-torque situation, including both an electronic current limit and mechanical overtorque coupling that automatically disengages the motor in an over-torque situation (Fig. 2.16).

Fig. 2.14 Side stuffer attached to TSE

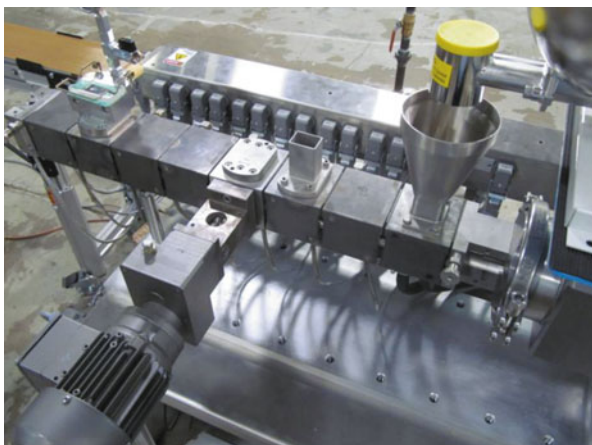
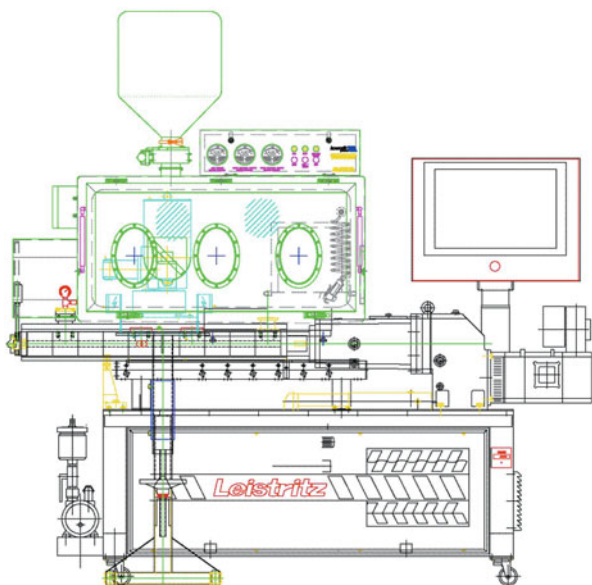


Fig. 2.15 Twin screw extruder with isolator containment system for API feed stream

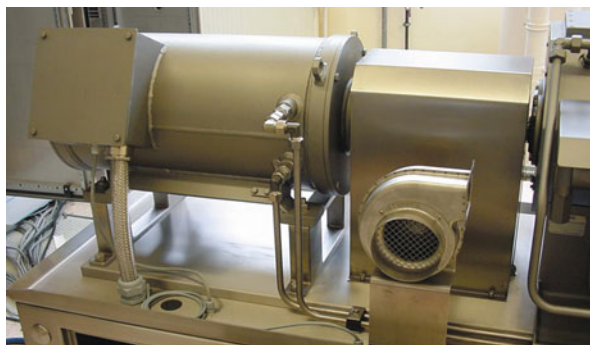


The TSE motor inputs energy into the process via rotating screws that impart shear and energy into the materials being processed. Alternating current (AC) motors/drives utilize digital communications, and can upload/download drive settings. The percentage motor torque is a particularly critical parameter to be monitored, and is measured as follows:

% Torque This formula indicates the percentage of available rotational force (screws) being used in a process, and is a typical readout denoted as a percentage that is calculated as follows:

$$\% \text{ Torque} = \text{Applied KW} / \text{Maximum KW}$$

Fig. 2.16 Water-cooled motor attached to over-torque coupling and TSE gearbox



Unit

Kilowatt (KW) is the electrical current or load from the main motor.

For example, if a TSE has a maximum rating of 100 KW and a process draws 40 KW then the torque is 40 % (40 KW/100 KW).

$$\% \text{ Torque} = 40/100 = 40 \%$$

For quality control and process troubleshooting, specific energy (SE) is a particularly important parameter to monitor, and is calculated as follows:

Specific Energy Specific Energy is the amount of power that is being input by the motor into each kilogram of material being processed. It is important that SE records be maintained for quality assurance and troubleshooting purposes. SE can also be used as a benchmark for scale-up and/or comparing different manufacturing operations. SE is calculated in two steps:

Applied power can be calculated as:

$$\begin{aligned} \text{KW (applied)} &= \text{KW (motor rating)} \times \% \text{ torque} \times \text{rpm running/max. rpm} \\ &\times 0.97 \text{ (gearbox efficiency)} \end{aligned}$$

Now, the SE can be calculated as:

$$\text{Specific Energy} = \frac{\text{KW (applied)}}{\text{kg/h}}$$

Units

KW Kilowatts (the motor rating)

% Torque % used of the maximum allowable torque

Rpm Screw rotations per minute

SE is denoted in KW per kg/h.

For example:

A 40 mm TSE is processing an HPMCAS formulation at 30 kg/h, running at 100 rpm with 68 % torque. The machine has a 50 KW motor and a maximum screw rpm of 600.

$$\text{KW(applied)} = 50 \text{ KW} \times 0.68 \times 100/600 \times 0.97 = 5.8, \text{ then}$$

$$\text{SE} = 30/5.8 \text{ or } 0.195 \text{ KW/kg/h.}$$

If the 0.195 SE suddenly changed to 0.25 or 0.15 and the process conditions were the same, it would indicate that either the material or hardware had significantly changed, and that the production of that batch should be discontinued until the problem was identified and corrected.

TSEs are available with top screw rpms of 1,200 or higher. The TSE should not be geared substantially higher than the required screw rpm, particularly for TSEs with ODs of 40 mm and larger. Due to the heat/shear-sensitive nature of many pharmaceutical formulations, the motors and gearbox are often specified for top screw speeds of 500 rpm or lower.

The following formula can be used as a guideline on how to configure the motor/gearbox:

Shaft Torque as It Relates to Screw rpm The cross-sectional area of the screw shafts, the shaft design/metallurgy, and the manufacturing method determines the torque that can be imparted into a process. This formula helps determine the proper motor and gearbox configuration for a TSE:

$$\text{Torque} = 9,550 \times \text{KW/top rpm}$$

Units

9,550 Constant

Torque Total torque for both screw shafts, typically denoted in Nm (Newton meters)

KW Motor rating on the TSE

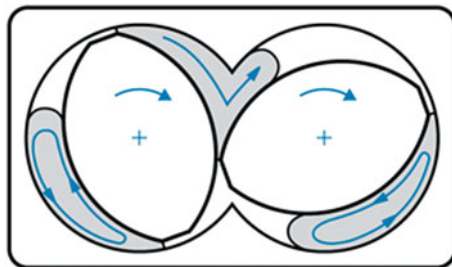
For example:

If a TSE with 30 mm OD screws has a torque rating of 318 Nm, and therefore uses a 20 KW motor at full torque if geared for 600 rpm. A 40 KW motor would be specified at 1,200 rpm at full torque as indicated in the following comparison:

$$318 = \frac{9,550 \times 20}{600} \quad 318 = \frac{9,500 \times 40}{1,200}$$

If a process has been defined and it has been determined that TSE will never operate above 400 rpm, then it should not be geared for 1,200. Since the torque is a constant, a 30 mm TSE can either be geared at 400 rpm with a 15 kW motor (13 kW applied), or at 1,200 rpm with a 40 kW motor (or with another motor/gearbox combination). In most instances, high rpms will not be specified for pharmaceutical applications, unless the TSE is intended for research and future usage is unknown (Martin 2006).

Fig. 2.17 TSE Bilobal co-rotating, intermeshing screws—“self-wiping”



2.3 TSE Process Section: the “Key” to Success

The heart of the TSE is its screws and barrels, referred to as the process section. Screws and barrels are often manufactured of hardenable stainless steels. Nickel-based alloys are specified for corrosive process environments. The metallurgies selected must not be additive, reactive, or absorptive with the materials being processed to be used in a pharmaceutical class environment. Cleaning and storage protocols must be adhered to when handling TSE parts.

In a co-rotating, intermeshing TSE, the screws are termed “self-wiping”. The surface velocities of the screws in the intermesh region are in opposing directions, which results in the materials being “wiped” and forced to follow a figure 8 pattern down the length of the screws. Most co-rotating TSEs are bilobal, referring to the number of “lobes” that are possible at a given OD/ID ratio (Fig. 2.17).

The heart of the high-speed TSE is its screws. There are seemingly an infinite number of screw variations possible. There are, however, only three basic types of screw elements: flighted elements, mixing elements, and zoning elements. Flighted elements forward material past barrel ports, through mixers and out of the extruder to pressurize the die. Zoning elements isolate two unit operations. Screw designs can be made shear-intensive or passive, based upon the elements used in the design.

Mixing elements can be dispersive and/or distributive, or a combination thereof. The kneader is the most prevalent mixing element used in a TSE. The wider a kneader is the more dispersive it becomes as extensional and planar shear effects occur as materials are forced up and over the land. Narrower kneaders are more distributive in nature that force high melt division rates with significantly less extensional and planar shear effects. Distributive mixing elements can be particularly useful for mixing heat- and shear-sensitive materials. Kneading elements can be arranged with a forward pitch (less aggressive), neutral, or reverse pitch (most aggressive). High liquid phase mixing generally benefits from specialty distributive elements that prevent “pooling” of the liquids in the TSE process section (Martin 2001; Fig. 2.18).

Counterrotating intermeshing TSEs are also viable for pharmaceutical applications. Looking into the feed throat, the screws rotate outward that results in feeding on both screws. In the screw intermesh region, the flight of one of the screws penetrates the flight depth of the second screw, and the velocity of the screws in the intermesh is in the same direction. This region is referred to as the calender gap. Screw rotation

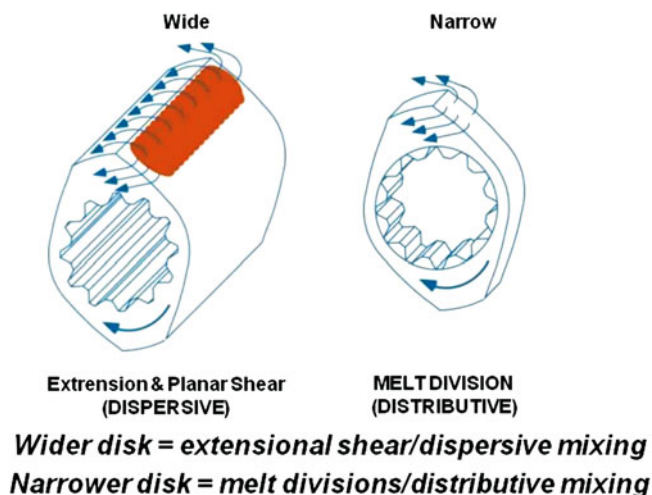


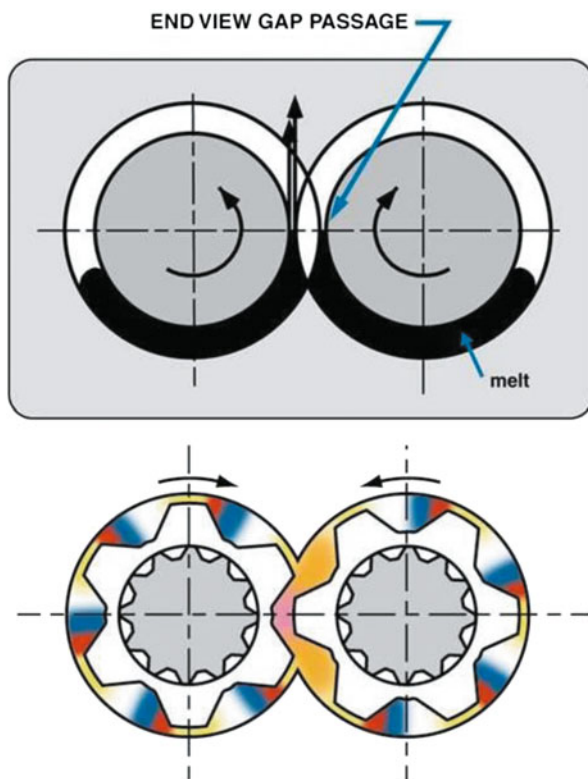
Fig. 2.18 Example of dispersive and distributive mixing elements.

forces materials up and through the calender gap to facilitate melting and mixing as the processed materials experience an extensional mixing effect. Essentially, the entire length of the screw can function as a mixing device as materials continually experience the extensional mixing and shear associated with the calender gap. In addition to calender gap mixing, gear mixers can be utilized for distributive mixing, as well as blister rings for planar shear mixing and/or to provide a seal for vacuum venting. At the discharge end of the screws, positive displacement pumping elements can be specified that pump in a C-locked chamber. Because of screw deflection inherent with the materials being forced through the calender gap, the top screw rpms are typically lower as compared to co-rotating TSEs. In counterrotation, hexalobal mixers are possible at the same flight depth as in bilobal co-rotating TSE designs, which translates into more possible mixing events for each screw rotation (Martin 2005; Fig. 2.19).

TSEs are also efficient as a means to purify the melt stream, referred to as devolatilization which occurs via vents in the TSE process section (Fig. 2.20). Factors that impact devolatilizing efficiency are: Residence time (RT) under the vent or vents (longer the better), surface area of the melt pool (higher the better), and surface renewal (higher the better). Single or sequential atmospheric- and/or vacuum pump-assisted vents can be integrated into the TSE design (Fig. 2.21). The type of pump and vacuum system design depends upon the level and type of volatiles being removed. It is possible to remove more than 20 % volatiles (or more) in a TSE process (an example is the removal of 20 % water from a thermoplastic starch slurry via four vents). Increasing the screw rpm and/or decreasing the rate generally improves devolatilization efficiencies, and the use of stripping agents (i.e., supercritical CO₂) can be utilized to achieve near zero residual levels (Martin 2001).

State-of-the-art TSE barrels are sequential, modular blocks and typically use electric cartridge heaters and internal bores for liquid cooling. Barrels can also use liquid

Fig. 2.19 Example of counterrotating calender gap and hexalobal mixing elements



temperature controls. Various types of barrels are available and matched to the unit operations being performed in that region of the process section. Increasing the coolant flow and heat transfer capabilities of the barrels is beneficial for heat-sensitive APIs. Just like screws, hardened stainless steels are adequate for most processes, while nickel-based alloys are specified for corrosive resistance (Fig. 2.22).

Barrel sections are available in two basic configurations: sequential blocks and clam shell, providing unique advantages and disadvantages. Clam shell designs allow for the barrel to be opened, analogous to opening a clam and hence the name of

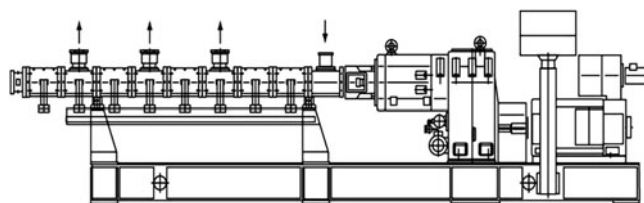


Fig. 2.20 Multistage venting and devolatilization factors

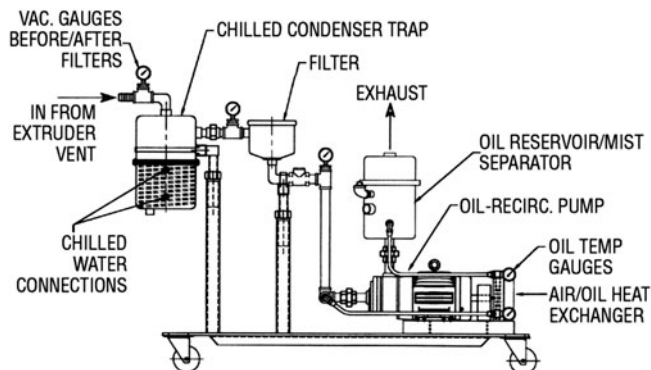


Fig. 2.21 Schematic of a vacuum pump

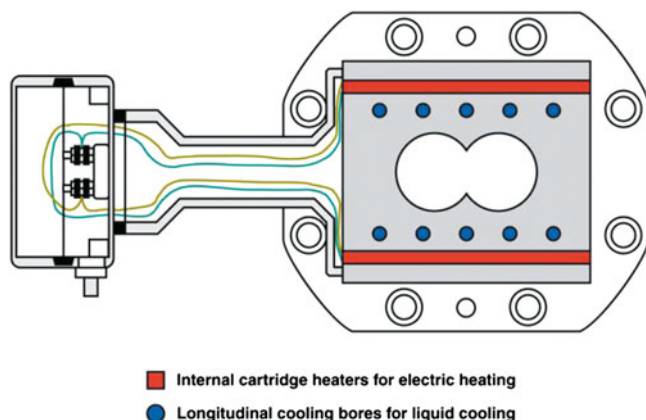
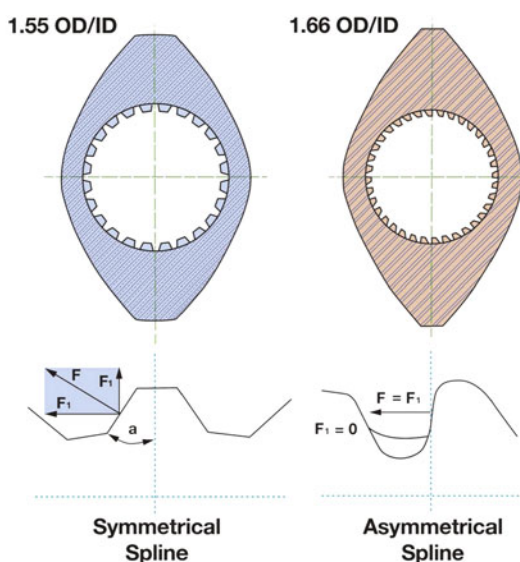


Fig. 2.22 End view of TSE barrel heating/cooling design

the design. This allows users to easily access all points of the barrel for sampling and cleaning activities, which can be advantageous by allowing for regional determination of process performance without removal of the screws from the barrel. Modular interchangeability with these systems is often more limited when compared to the sequential block design. Also, leakage along the barrel seam is possible for high-pressure operations, which is less likely with other barrel geometries. Temperature control is also generally not as precise with the clam shell design. In the case of the sequential block design, modularity of the system and temperature are improved. Locational sampling along the length of the extruder requires specific shut-down, cooling, and screw removal protocols for equivalency to the clam shell design.

As previously stated, the OD/ID ratio of a TSE is defined by dividing the outside diameter (OD) by the inside diameter (ID) of each screw. For instance, a TSE with an OD of 50 mm and an ID of 30 mm would have an OD/ID ratio of 1.66 (50/30). The torque limiting factor for a TSE is the screw shaft diameter and design. Deeper screw

Fig. 2.23 End view of 1.55 and 1.66 OD/ID screw element geometries with comparative symmetrical and asymmetrical shaft design (1 tooth)



Smaller diameter shaft can transmit more torque

flights result in more free volume, but with less torque, since a smaller diameter screw shaft is mandated. Based on the use of a symmetrical splined shaft, a 1.55 OD/ID ratio has been deemed to offer the best balance of torque and volume. The use of asymmetrical splined shafts improves the power transmission efficiency of the shaft so that a smaller diameter shaft can transmit higher torque since the tangential force vector from the shaft tooth is isolated and therefore more efficient in transmitting power from the motor into the shafts/screws/materials being processed. The use of an asymmetrical splined shaft facilitates an increased OD/ID ratio of 1.66/1 with increased torque (Fig. 2.23).

A higher OD/ID ratio (i.e., 1.66/1 vs. 1.55/1 OD/ID) results in both a deeper channel and narrower kneader crest. The materials that pass over the kneader tip experience less RT in planar shear. Both factors contribute to a lower average shear rate inherent with a deeper-flighted TSE, which is often beneficial for processing shear-sensitive formulations (Martin 2012b).

As previously stated, L/D ratios for pharmaceutical processes range from 20/1 for a premix feed to 50/1+ L/D for some injection and solvent extraction processes. Whatever the OD/ID and L/D ratio, it is important to know the specific volume of the TSE:

Specific Volume Specific volume (SV) represents the approximate volume for 1 L/D of the process section, which is useful in a number of other formulas.

$$\text{Specific Volume} = 0.94 \times (\text{OD}^2 - \text{ID}^2) \times \text{OD}/1000$$

Units:

SV is denoted in cc/diameter of length

OD Screw outside diameter (each)

ID Screw inside diameter (each)

For example:

For a HSEI-TSE with a screw OD of 50 and an ID of 30 mm (a 1.66 OD/ID ratio), the approximate SV is as follows:

$$SV = 0.94 \times (50^2 - 30^2) \times 50/1000 = 75.2 \text{ cc/dia}$$

Residence Time This formula provides the approximate residence time (RT) in the process section. It is important to note that the residence time distribution (RTD) is dependent upon the degree of screw fill. The following formula can be used for RT:
Step 1: Calculate degree of fill in TSE process section:

$$\% \text{ Fill} = \frac{\text{Rate} \times 0.2777}{\text{FV} \times (\text{Run rpm}/60) \times \text{SG} \times 0.35} \times 100$$

Units:

Rate kg/h

FV Free volume of the extruder, in cc/dia

SG Specific gravity

Run rpm Operating screw rpm

For example:

A 50 mm extruder with a FV of 70 cc/dia., processing 100 kg/h at 200 screw rpm with a 1.0 SG:

$$\% \text{ Fill} = \frac{100 \times 0.2777}{70 \times (200/60) \times 1.0 \times 0.35} \times 100$$

$$\% \text{ Fill} = 34 \%$$

Step 2:

$$\text{Residence Time (RT)} = \frac{L/D \times 0.28}{\% \text{ Fill}} + (\text{MP} \times 14.5 \times 0.01)$$

Units:

RT Residence time in seconds

SG Specific gravity

L/D Length/diameter ratio of extruder

0.28 is a composite forwarding efficiency for the screws

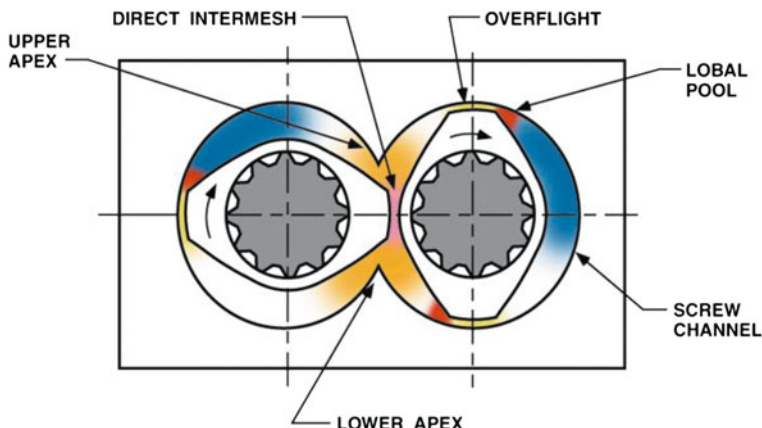


Fig. 2.24 End view of the five TSE mass transfer regions

% Fill Degree of fill, expressed as a decimal (i.e., 40 % = 0.4; dependent on screw design)

MP Melt pressure in Bar

For example:

A 50 mm extruder with a 40 L/D processing 100 kg/h with a 1.0 SG with a 34 % screw fill (0.34), with a 20 Bar outlet pressure, the following applies:

$$RT \text{ (average)} = \frac{(1.0 \times 40 \times 0.28)}{(0.34)} + (20 \times 14.5 \times 0.01)$$

$$RT \text{ (average)} = 35.8 \text{ s}$$

Note: This is a rough approximation and can be made more accurate by adjusting the forwarding efficiency constant based upon experimental results. Also, the residence time distribution (RTD) will be highly dependent upon the degree of screw fill.

In any TSE, there are five shear regions inherent with the screws (Fig. 2.24):

- *Channel region* is a low shear region and is dependent on the degree of screw fill in a starve-fed TSE. The mixing rate in the channel in a TSE is significantly lower as compared to the other shear regions.
- *Overflight gap region* is a high shear region and is independent of the degree of screw fill. This is the area between the screw tip and the barrel wall where the material experiences planar shear.
- *Extensional mixing region* is a high shear region and is independent of the degree of screw fill. This is the area where the material accelerates/experiences a mixing effect from the channel entering into the overflight gap.
- *Apex (upper/lower) region* is a high shear region and is independent of the degree of screw fill. This is where the interaction from the second screw results in mixing due to the associated pressure fields, compression/expansion of the melt, and directional flow changes.

- *Intermesh region* is a high shear region and is independent of the degree of screw fill. This is the area between the screws; in co-rotation the screw surface velocities are in the opposite direction, and in counterrotation the same direction.

It is worth noting that the four high mass transfer regions can, to a certain extent, be considered independent of the degree of screw fill. This partially explains why, in a starve-fed TSE, when the throughput rate is decreased at a constant screw rpm, more mixing occurs, as the materials being processed have a longer RT in the mixing zones. Conversely, as the throughput rate is increased, the low shear channel region dominates more, and the materials being processed will spend less time in the mixing zones (Martin 2001).

The following are some additional formulas that provide insight into any TSE process:

Peak Shear and Shear Stress The peak shear can be critical to achieve dispersive mixing, and can also result in degradation. The following provides a benchmark for the peak shear in a TSE:

$$\text{Peak shear rate} = (\pi * D * n) / (h * 60)$$

Units:

D Screw diameter

n Screw rpm

h Overflight gap

Hence, for a TSE with a 27 mm OD screw and 0.1 mm overflight gap operated at 600 rpm, the peak shear would be calculated as follows:

$$\text{ZSE-27} = \frac{(\pi * 27 * 600)}{(0.1 * 60)} = 8478/\text{s}$$

The formula can be used as a rough estimate to match rpms for TSEs with different diameters, or to estimate the peak shear at a particular rpm. Peak shear rate can be used to calculate shear stress, which is the critical factor to accomplish dispersive mixing:

$$\text{Shear stress} = \text{Peak shear rate} \times \text{Viscosity}$$

In the early stages of the TSE process section, viscosities are higher and high stress rates are produced that cause dispersive mixing (or degradation). In the later stages of the TSE process section, the viscosities typically decrease and result in comparatively lower stress rates. Increased cooling can be used as a tool to increase the viscosity of the melt to achieve dispersive mixing. It must be noted that shear stress calculation does not reflect and is not a measurement of extensional shear, which is much more complicated to calculate and requires modeling, but does provide a benchmark and insight into the dispersive mixing effect.

Fill % Approximation This formula provides the percentage of the available volume in the process section that is being utilized in the starve-fed TSE

$$\% \text{ fill} = \frac{Q \times 0.2777}{SV \times \text{rpm}/60 \times SG \times Ef}$$

where

Q Flow rate in kg/h

Ef Average forwarding efficiency (approx. 35 % for a screw with 1/3 kneaders and 2/3 flighted elements, or 0.35)

SV Specific volume of extruder in cc/dia

rpm Screw rpm

SG Specific gravity of the material being processed

For example, a 40 mm extruder with an SV of 35 cc/dia is running 30 kg/h at 100 rpm,

$$\% \text{ fill} = \frac{30 \times 0.2777}{35 \times (100/60) \times 1.0 \times 0.35} = 0.41 \text{ or } 41 \% \text{ filled}$$

This calculation might show that a process that is devolatilization intensive (i.e., for solvent extraction) is run with a 30 % degree of screw fill because a starved process section increases the surface area of the melt pools under the vent or vents. Another example might demonstrate that a shear-sensitive process might run with a 60 % degree of screw fill.

This formula is a rough estimation and is meant to provide insight into the dynamics of a starve-fed TSE process section, as compared to an absolute value. More advanced/accurate models are available that take into account the specific screw geometries, the viscosity of the melt, and the degree of screw fill.

What is known is that higher fill levels result in a tighter RTD and less shear intensity, with lower fill levels associated with a wider RTD and more shear intensity (Fig. 2.25). Fill level approximations help explain why processes benefit from different feed rates versus screw rpms.

Scale-Up Formula Scale-up is useful for estimating rates for future production TSEs based on lab-scale experiments. The geometries for the two extruders (OD/ID and L/D ratios) should be similar for this equation to be valid. For processes that scale-up volumetrically, the formula is as follows:

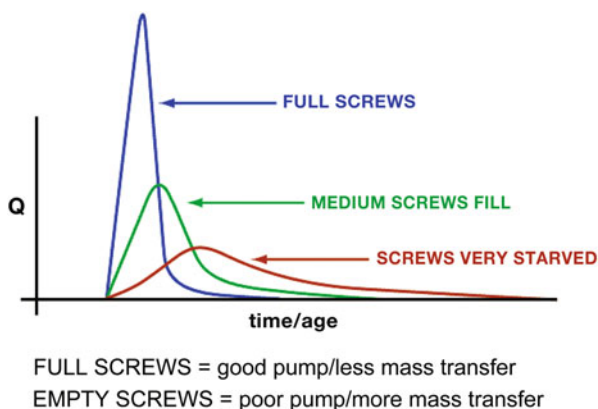
$$\text{Scale up: } Q_{\text{target}} = Q_{\text{reference}} \times \left[\frac{OD_{\text{target}}}{OD_{\text{reference}}} \right]^3$$

Units:

Q Throughput rate (in any units)

OD Screw outside diameter (each)

Fig. 2.25 Residence time distribution comparison for various levels of screw fill



For example:

A 18 mm TSE is producing 2 kg/h and the process is not limited by heat transfer or mass transfer boundary conditions. To estimate how much a 40 mm TSE will produce, the following calculations will apply:

$$Q(18 \text{ mm}) = 2 \times (40/18)^3$$

$$Q(40 \text{ mm}) = 2 \times 2.22^3 = 22 \text{ kg/h}$$

For a heat transfer limited process, the exponent in the scale-up formula is closer to 2. For devolatilization and many pharmaceutical processes, the scale-up exponent is between 2.3 and 2.5. The greater the difference in extruder ODs, the less reliable this calculation becomes. Advanced formulas and computer modeling approaches are also available for more intensive scale-up work (Martin 2006).

How the TSE is configured and operated makes the difference between success and failure. In addition to the process section design (screws/barrels), feed rate, screw rpm, temperatures, and sequence/location of feed streams all play a role in the shear intensity to which the materials are exposed. Table 2.1 provides a brief overview of how a pharmaceutical, or any, TSE process can be managed.

The balance between the rate set by feeders and the screw rpm is obviously important for managing the process intensity and shear history. Process temperatures and the screw design also play critical roles. Everything must work together to optimize the final product (Thiele 2003).

The quality of the product is often affected by the melt temperature of the extrudate, which is often highly impacted by the front-end pressure of the TSE. Front-end management of the melt stream can make the difference between success and failure of a process.

Temperature Rise Caused by Pressure Pressure generation in the extruder front-end results in a temperature rise. The more restrictive the front-end, the higher is the pressure and melt temperature rise, which often adversely effects product quality. The temperature rise formula is as follows:

$$\Delta T (^{\circ}\text{C}) = \frac{\Delta P (\text{bar})}{2}$$

Table 2.1 Conditions regulating process intensity

Type of processing	Gentle	Strong
Screw speed	Low	High
Mixing rate in each of the mass transfer along the screws is proportional to rpm		
Screw fill	High	Low
Starving the feed increases remastication and time in mixers to increase process intensity		
Temperature	High	Low
Lowering the temperature increases the controlling modulus and dispersive stress rate		
Extensional/planar mixing	Low	High
Increasing the number of lobal events (i.e., rpms) increases process severity		
Sequential feed	Depends	Depends
Sequential feed may be employed to either utilize or avoid high stress rate exposure		

Units:

ΔT Change in temperature in $^{\circ}\text{C}$

ΔP Change in pressure (1 bar = 14.503 psi)

For example:

If the die pressure is 40 bar then the associated melt temperature rise can be 20°C . ($\Delta T = 40/2$)

This formula is meant to be insightful, if not necessarily accurate, as TSE rpm, geometry of the discharge screw elements, and formulation viscosity all play significant factors in the actual melt temperature.

2.4 Downstream Systems

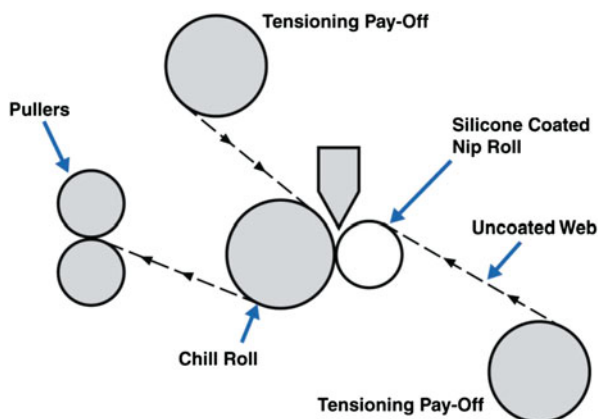
A wide variety of downstream systems are available to extrude an infinite array of pellets and/or shapes. Pelletization is a process where the melt stream is pumped through a die, cooled and formed into a pellet, typically between 0.5 and 5 mm. In strand pelletization, “spaghetti” strands are extruded and cooled on a stainless steel or plastic belt conveyer. The pelletizer feed rolls pull the strands and push them into the cutting assembly. Smaller pellets can be used for direct capsule filling, whereas larger pellets are typically milled.

Die face pelletization is also common, where the pellets are cut at the die face and conveyed/cooled to air quenched chimneys and vibratory towers/trays. The advantage of this system, if workable, is that strand breakage during the cooling phase is

Fig. 2.26 Micro-pelletizer attached to TSE



Fig. 2.27 Schematic of lamination system



eliminated. Die face pelletizing is not as wide spectrum with regard to the range of materials that can be processed, and start-up procedures need to be carefully defined and repeated. However, if the process is amenable, die face pelletizing is often preferred to strand systems (Case and Martin 2005; Fig. 2.26).

Film and lamination systems are often used to produce transdermal and dissolvable films (Fig. 2.27). To maintain dimensional tolerances, a gear pump (or screw pump) that builds/stabilizes pressure to the die is often specified. A gear pump is a positive displacement melt delivery device that builds and stabilizes the melt stream from the TSE and into the die. The melt is then distributed in a flat die and cooled on rolls. The roll surface is maintained at the desired temperature by liquid circulating through internal cooling channels. For some flat products the nip force across the roll face is used to “squeeze” the extrudate between the rolls. Unwind stations can be

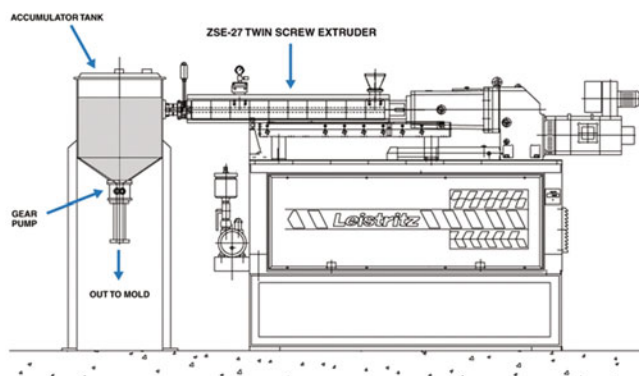


Fig. 2.28 Continuous compounding combined with in-line molding system

utilized to laminate the film onto a substrate. The final product is then either wound or cut-to-length.

Shape extrusion is when the process melt is directly extruded into a part with specific dimensions. Unique shapes are possible. The extrudate can be a simple rod, or complex shape, referred to as a “profile”. The extruded profile is formed in the die, sized by calibration tooling, and conveyed and supported through a variety of different types of air cooling devices. A belt puller pulls the extrudate and then feeds it to an on-demand or flywheel type cutter. In this manner, for example, a pre-form tablet might be produced (Elliott 2003).

In-line molding is also possible to produce unique three-dimensional dosage forms (Fig. 2.28). In this operation, the formulation is mixed and devolatilized in a TSE and discharged into an accumulator. A gear pump or screw pump then operates cyclically to fill a mold that determines the final product shape and dimensions. This process is highly formulation-dependent.

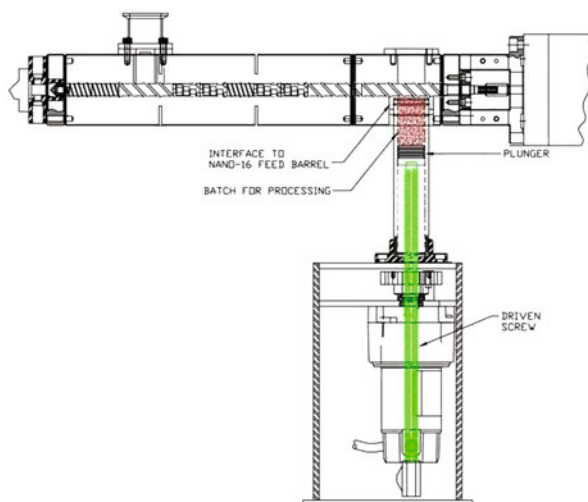
2.5 Examples of Pharmaceutical Processes Performed on Twin Screw Extrusion Systems

The following provides a few examples of related processes/applications:

2.5.1 Nano-16 Twin Screw Extrusion System Case Study

A challenge in the early stages of development is that APIs are expensive and only available in limited quantities. Hence, a need arose to process very small samples (between 20 and 100 g) via ME. Therefore, a low volume TSE with 16 mm OD

Fig. 2.29 Micro-plunger feeder attached to low-volume TSE



screws and a 1 mm flight depth with a 1.2/1 OD/ID ratio and 1 cc/dia free volume was used to process a series of 50 g batch samples of a HPMCAS polymer with 40 % of a poorly soluble API. The objective was to demonstrate the viability of the extrusion process utilizing a small sample with minimal waste. The materials were premixed and metered by a patented micro-plunger feeder (Fig. 2.29). A 25–1 L/D process section was utilized. The screw design included flighted elements and kneading/shear-inducing elements. An atmospheric vent and a low-volume strand die front-end attachment were used.

Approximately 44 g of the sample was collected and usable for evaluation purposes. Approximately 6 g of material was “lost” in the TSE process section as follows: 1 g at the extruder/plunger interface, 2–3 g on the screws, and 2 g in the die/front end. The temperature profile and screw rpms were selected based upon experience with similar formulations. A PC-based control/data acquisition package allowed for detailed analysis of the run conditions (Fig. 2.30).

The strand was cooled in an air-quenched annular chamber, cut into 1 mm pellets, and collected. The pellets were then milled into a powder and compressed into tablets for dissolution testing. The results indicated that the API was converted from a crystalline to amorphous state during processing. Without extrusion, this API might not have been a candidate for additional development (Fig. 2.31).

Subsequent tests were performed at 2 kg/h (TSE with 18 mm screw diameter) and 6 kg/h (TSE with 27 mm screw diameter) with similar results, confirming the viability of the initial screening device (Martin 2010).

2.5.2 Melt Granulation

Melt granulation has traditionally been performed by a high-shear granulator with double-jacketed granulation bowl, where either water or oil is circulated as the

Run Data										
Runtime	Z1	Z2	Z3	Z4	Z5	A1	A2	A3	A4	A5
0:00:00	120	125	130	131	131	0	0	86	53	0
0:01:00	120	125	130	131	130	100	2	207	190	0.27
0:02:00	120	125	130	130	130	100	2	138	179	0.45
0:03:00	120	125	130	130	129	100	2	207	203	0.63
0:04:00	120	125	130	130	128	100	2	466	266	0.87
0:05:00	120	125	130	130	127	100	2	742	303	1.17
0:06:00	120	125	130	130	126	100	2	760	314	1.48
0:07:00	120	125	130	130	125	100	2	673	314	1.79
0:08:00	120	125	130	130	124	100	2	742	324	2.1
0:09:00	120	125	130	130	124	100	2	725	324	2.43
0:10:00	120	125	130	130	123	100	2	1019	385	2.79
0:11:00	120	125	130	130	123	100	2	1019	409	3.19
0:12:00	120	125	130	130	122	100	2	1036	401	3.6
0:13:00	120	125	130	130	122	100	2	932	374	3.98
0:14:00	120	125	130	130	122	100	2	1036	390	4.36
0:15:00	120	125	130	130	122	100	2	1088	398	4.77
0:16:00	120	125	130	130	121	100	2	1071	409	5.19
0:17:00	120	125	130	130	121	100	2	1209	443	5.62
0:18:00	120	125	130	130	121	100	2	1226	467	6.07
0:19:00	120	125	130	130	121	100	2	1140	427	6.51
0:20:00	120	125	130	130	121	100	2	1105	417	6.94
0:21:00	120	125	130	130	121	100	2	1157	459	7.37
0:22:00	120	125	130	130	121	100	2	1278	475	7.82
0:23:00	120	125	130	130	121	100	2	1364	496	8.31
0:24:00	120	125	130	130	121	100	2	1519	511	8.82
0:25:00	120	125	130	130	121	100	2	1347	525	9.32
0:26:00	120	125	130	130	121	100	2	1312	469	9.82
0:27:00	120	125	130	130	121	100	2	1450	562	10.31
0:28:00	120	125	130	130	121	100	2	1485	525	10.83
0:29:00	120	125	130	130	121	100	2	1416	506	11.35
0:30:00	120	125	130	130	121	100	2	1416	509	11.86
0:31:00	120	125	130	130	121	100	2	1381	546	12.35
0:32:00	120	125	130	130	121	100	2	1381	509	12.86
0:33:00	120	125	130	130	121	100	2	1329	485	13.36
0:34:00	120	125	130	130	121	100	0	1220	448	13.72
	Z1 = Zone 1 Temperature					A1 = Screw Speed				
	Z2 = Zone 2 Temperature					A2 = Plunger Feeder cc/min				
	Z3 = Zone 3 Temperature					A3 = Pressure				
	Z4 = Zone 4 Temperature					A4 = Torque				
	Z5 = Melt Temp					A5 = TTQ				

Fig. 2.30 Nano-16 TSE process conditions/run record

heating medium. The disadvantages of this process include: inefficient processing due to the slow heat transfer from the bowl to the powder blend, difficulty in process scale-up since the area of the heated surface to the volume of powder blend

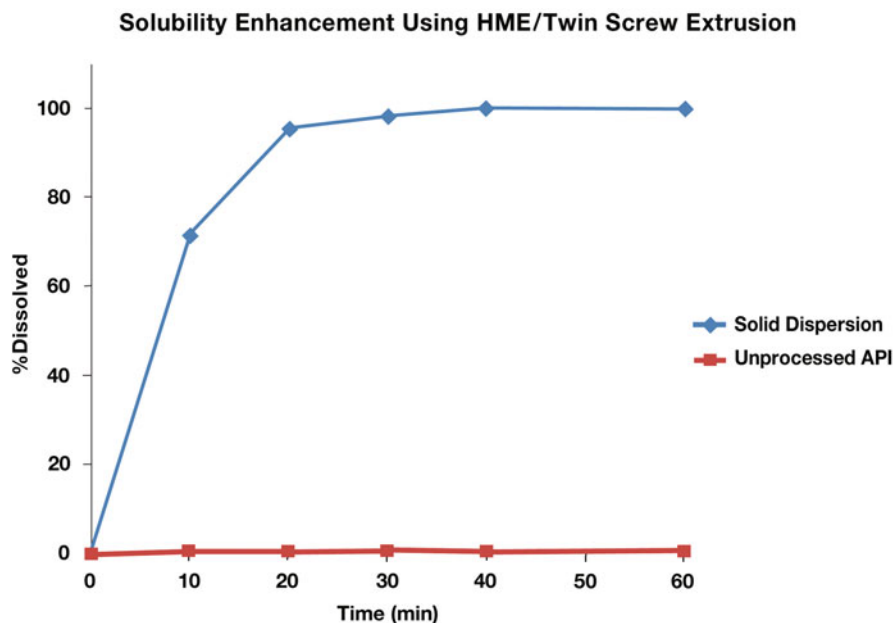


Fig. 2.31 Nano-16 sample results from dissolution testing

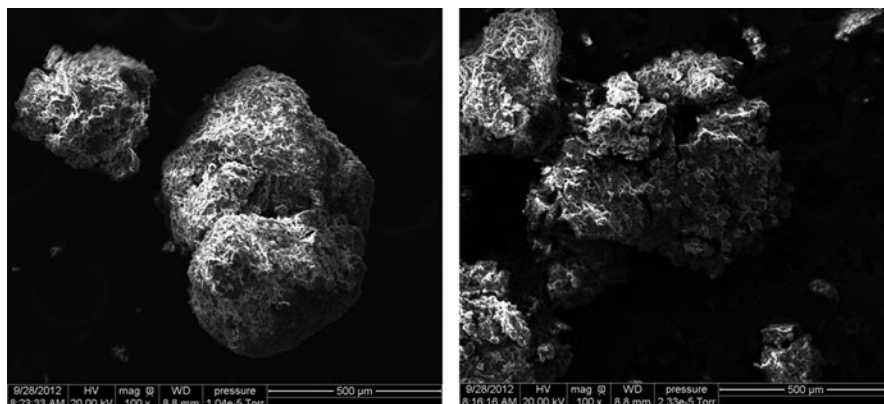
decreases with an increase in batch size, and batch-to-batch variability associated with inconsistent heat transfer.

A powdered premix was metered into a TSE with a 16 mm OD. The mechanical energy of co-rotating TSE screws, rather than the heat conducted from the barrels, melted/softened the premix with minimal heat transfer between the extruder barrel and materials. A binder that melted at a relatively low temperature (60–80 °C) was used to achieve the agglomeration of the formulation composition. During extrusion, the formulation was subjected to high pressure which resulted in granules with a higher density and better flowability in comparison with the granules from a high-shear granulator. An air quench front-end with mild compression helped optimize granule formation. The granules were formed after the material exited the die and the molten binders solidified.

Through the use of TSE melt granulation highly compressible granules were produced that yielded tablets with minimal weight variation. It can also be theorized that the TSE melt granulation with controlled/repeatable mechanically driven melting and short mass transfer distances is easier to scale-up as compared to a high-shear granulator (Keen et al. 2012; Fig. 2.32).

2.5.3 Micro-Pelletization for Capsule Filling

A EudragitTM polymer/API powdered premix was metered by an LIW feeder into a an 18 mm TSE that mixed, devolatilized, and conditioned the materials and pressurized

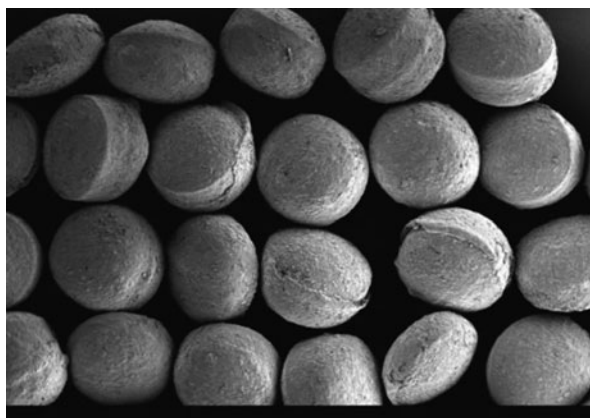


15% tramadol HCl granules
obtained by continuous melt
granulation with NANO16

15% tramadol HCl granules
obtained by melt mixing and
grinding through No. 20 mesh

Fig. 2.32 Melt granulation morphology produced from TSE

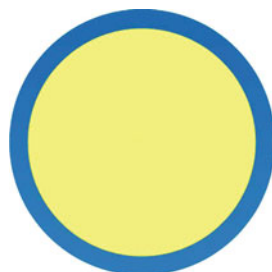
Fig. 2.33 Eudragit™ 0.5 mm
micro-pellets produced from
TSE



the inlet of a gear pump front-end attachment that built/stabilized pressure to an annular die with a series of 0.5 mm micro-die holes (Fig. 2.33). A differential pressure before/after the gear pump of 100 bar was required for this particular formulation to keep the micro-die holes from getting blocked. Rotating blades cut the strands at the die face that were then vacuum-conveyed to a cooling chimney which finished the cooling process and discharged the micro-pellets.

It should be noted that die face pelletizing can be problematic because some formulations will smear at the die face during cutting, and pellets may also have a tendency to stick together in the cutting chamber. Micro-pelletizing is particularly challenging as holes tend to get blocked and high pressures are often a requirement. For success, extensive formulation and process development can be expected (Elliott 2003).

Fig. 2.34 End view of coextruded structure rod/profile for sustained release of product



2.5.4 Thermo-Plastic Urethane (TPU) Coextruded Rod System

A thermo-plastic urethane (TPU) was premixed with a low percentage of API and metered into a TSE (27 mm OD screws) by an LIW feeder. The TSE process section design facilitated intimate mixing without over-shearing the TPU/API formulation. A gear pump was attached to the TSE to pressurize a coextrusion die. A single screw extruder (SSE) with 25 mm OD melted/conditioned a “virgin” TPU and was mated to and pressurized the same coextrusion die. The SSE is a flood-fed device that is used to melt and pump a precompounded material where the screw rpm determines the rate of the melt stream being fed into the die. The coextrusion die distributed the TPU melt from the SSE so that it completely encapsulated the inner TPU core that contained the active drug.

Since the inner core of the TPU coex structure was encapsulated, it was possible to pass the part through a water trough with guide rolls for more efficient cooling, as compared to air. If it was deemed that the structure could not contact water, then a series of driven/contoured rollers might be specified to cool the product. A precision belt puller pulled the extrudate through the water trough and fed an on-demand cutter that cut the extrudate into approx. 75 mm lengths. Longer or shorter lengths are possible. The parts were candidates to be post welded, as might be used as a vaginal ring. Flywheel type cutters can also be used to produce shorter length parts, i.e., in the 0.5 to 3 mm range (Fig. 2.34).

2.5.5 Transdermal Sheet/Laminate Extrusion

Multiple rubber feed streams were conditioned and metered into a TSE at a controlled rate. Rubbers are typically ground and fed into the TSE, or melted and pumped into the TSE. The API was metered by an LIW feeder into a side stuffer that pushed the API into the TSE process section. The materials were then mixed and discharged from the TSE into a gear pump that metered the melt stream to a flexible lip sheet die that distributed material across the die width. The downstream take-off was designed so that the nip force across the roll face “squeezed” the extrudate between the rolls, which were cored for liquid temperature control. Unwind stations, with electronic

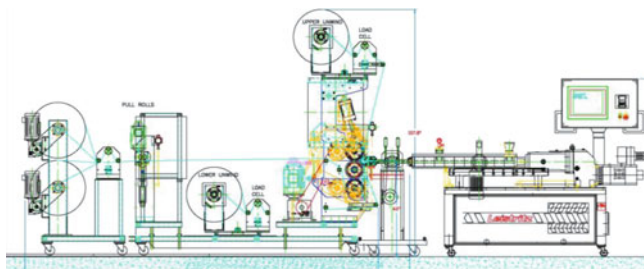


Fig. 2.35 Schematic of TSE transdermal-laminate system

tension control, introduced backing and peelable substrates and the extrudate together at the correct position to facilitate adhesion. An automatic cut-and-transfer winder was used to wind product prior to post-processing operations (DiNunzio et al. 2010; Fig. 2.35).

2.5.6 Extrusion of Foamed Extrudate

A EudragitTM polymer/API/talc were premixed and metered into a (27 mm OD screws) TSE by an LIW feeder. The materials were melted/mixed in the early stages of the TSE process section and dynamic seals were integrated into the screw design to accommodate high-pressure injection pressures inherent with supercritical CO₂. The supercritical CO₂ injection system was equipped with a precision piston type injection pump and chilled/temperature controlled plumbing connections. The supercritical fluid was injected and intimately mixed with the molten extrudate via high division distributive mixers to minimize viscous heating. The latter part of the TSE process screw design utilized low energy input pumping elements to allow the TSE barrels to serve as a heat exchange device to cool the process melt stream. The extrudate was pumped through a pelletization die, cut at the die face by rotating knives and vacuum conveyed to a cooling tower. The resulting foamed pellets were then milled and pressed into tablets that resulted in faster dissolution rates, indicating that by increasing the porosity of the matrices a faster acting dosage form is possible (Listro et al. 2012; Figs. 2.36 and 2.37).

2.5.7 Production ME System

A PVP/API premix was metered at 100 kg/h by an LIW feeder to a TSE (50 mm OD screws) that melted, intimately mixed, devolatilized, and pumped the formulation to a strand die. Vacuum venting was utilized to remove residual volatiles from the formulation. A 10-hole strand die was specified with an angle discharge onto a

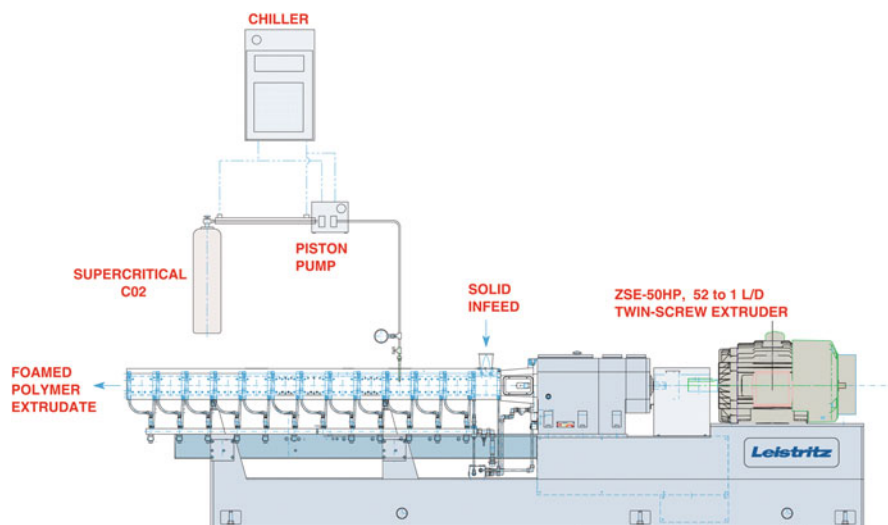


Fig. 2.36 Schematic of attachments of a TSE supercritical injection system

Fig. 2.37 Close-up of attachment “combing” mixing elements

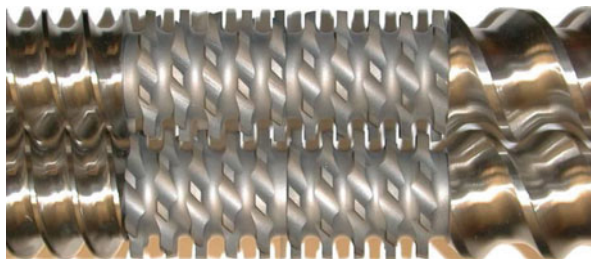


Fig. 2.38 Production class 50 mm TSE



stainless steel conveyor which cooled the strands which were then directly fed into a pelletizer and in-line mill. The temperature and speed of the cooling conveyor was critical so that the strands could be pelletized and cooled in-line (Fig. 2.38).

2.6 Summary/Conclusion

ME continues to evolve and create sophisticated dosage forms utilizing extrusion technologies that have already been developed in the plastics (and food) industries—extrusion is a battle-hardened, well-proven, manufacturing process that has been validated in 24 h/day industrial settings making the plastic products we see and use every day. Now that the pharmaceutical industry has embraced ME, machinery suppliers have downsized and redesigned equipment to meet the requirement of cGMP environments. Additional efforts have also been made to design TSE systems to test early-stage materials available only in minimal quantities. Coextruded structures, utilizing multiple extruders, foamed products and integration with in-line molding are the next generation of development efforts that are foreseen.

The best indication of the future is the past. The plastics industry evolved from batch to continuous processing to make better, more consistent products at lower cost. This is now happening in the pharmaceutical industry. The future is bright for ME, and the path is well-proven.

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