IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Process Development And Scale-Up: Twin-Screw Extrusion

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Abstract

Extrusion technology is well known that has been developed over the last century and spans many diverse industrial fields. The main application of extrusion technology in the pharma field is of hot-melt extrusion. Hot-melt extrusion technique is utilized by much pharmaceutical industry for manufacturing various dosage forms. Many formulations developed using HME are introduced in the market. The twin-screw extrusion technology is used widely in hot melt processing. Various processing factors in twin-screw extruders impacts product quality. During the development of the HME process, one must consider drug and excipient's thermal profiles, barrel temperature, screw speed, and feed rate. Scaling up the extruder process is a critical task that requires an understanding of screw geometry, volumetric dimensions of the screw, the power required, and heat transfer and generation. Nowadays, simulation software like Ludovic and Polyflow have developed, which can mimic the product movement and heat distribution in extruder and help in scaling the process. The regulatory authority is these days enforcing quality by design approach, which applied to HME. As it is continuous, process monitoring at each step is an important part, and therefore process analytical tool as part of QbD are developed. NIR, RAMAN, UV spectrometry methods generally used. Many novel formulations have been developed using extruders. Therefore the proper understanding of scale-up and process design will provide insights to solve various formulation problems.

Keywords: twin-screw extruder, hot-melt extrusion, Ludovic, Polyflow, Process analytical tools.

2. Introduction

Extrusion technology is well known that has been developed over the last century and spans many diverse industrial fields. Extrusion which is defined as a process of forming a new material by forcing the content through an orifice or die under controlled condition. Historically extrusion technique was used in the food and plastic industry. Now is used to manufacture a wide range of industrial products like food products, plastics, chemicals, and now recently, pharmaceutical technology.

Extrusion equipment used in pharmaceutical industries is mainly two types. Single screw extruder and twin screw extruder.as the name itself implies. Single screw extruders use a single screw and twin arrangement; we have two screws usually arranged side by side. But widely used equipment is twin screw extruder due to various advantages, the shorter residence time, the stability of process, and the equipment size to achieve an equivalent output.

Twin-screw extrusion technology is used for various pharmaceutical processes, like Hot melt extrusion technology, melt granulation, and continuous wet granulation.
For these processes to designed and scaled up, the basic knowledge of the extruder design and its technical aspects are must be known as a formulation scientist. These basic parameters that affect the final product quality are must be controlled.

Twin-screw extruder is used for the hot-melt extrusion technique. Hot-melt extrusion technique is used to enhance the solubility of the poorly soluble drugs by preparing amorphous solid dispersions of drugs with that of polymers. This extruded can also be shaped, and thus various formulation can be developed. Tablets, soaps, films, pellets, etc. are prepared using this technique.

In the pharma industry most widely used granulation technique is wet granulation. Continuous wet granulation is performed in an extruder. Therefore batch variations are minimally seen. The proper screw design is selected, the binder is added using the feeder, and granules are collected and the end. Therefore material handling is not required which seems to be a significant problem in large scale manufacturing. Melt granulation a technique in which the binder of a low melting point is used melted in an extruder and then helps in the formation of granules, and many have tried using melt granules directly for compression purposes.

The scale-up approach must be totally focused on critical parameters; nowadays QBD approach is generally used during process development and actual production, so that product quality is maintained. Process analytical tools are used for in-process monitoring of twin-screw process methods like NIR, Raman and UV visible spectrometry is used as detection PAT tool.

Recently many software has been developed in which simulation of extruder processing is done and depending upon that, excipients are not only selected, but they have developed also.

2.1 Twin-screw extruder is most widely used in the pharmaceutical industry following are advantages over a single screw

a. They are self-cleaning , i.e., design can ensure that material is continuously exchanged on metal surfaces of the extruder and avoid stagnation.
b. They are used for continuous processes.
c. The short mass transfer distances within screw sections promote mixing accuracy and speed.

d. As it is a longitudinal process, one can sequence the process as per requirement.

2.2. Types of twin-screw extruders are as follows

a. Non-intermeshing counter-rotating twin-screw extruder
b. Intermeshing counter-rotating twin-screw
c. Intermeshing co-rotating

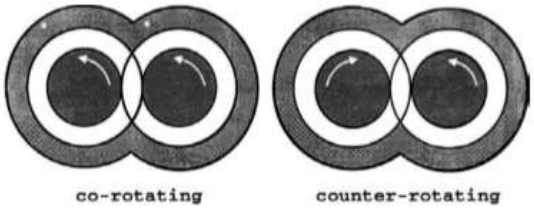


Figure 1. Corotating and counter rotating

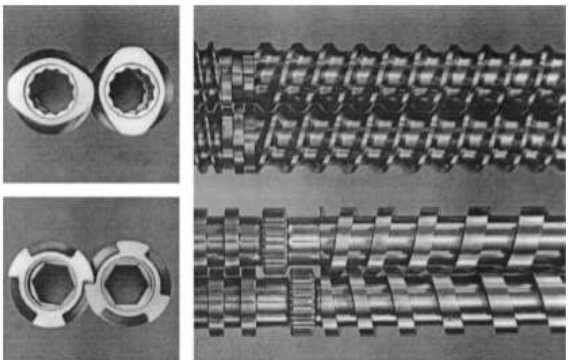


Figure 2: Intermeshing and Non intermeshing

3. Components of twin-screw extruder

3.1 Barrels

They are housing for the screw. The cooling of the barrel is done using water, and electrically heat is provided. Temperature can be control in groups or individually depending as per requirements.

Two types of barrels

a. One piece

b. Modular barrel - mainly used in the pharmaceutical industry due to their flexibility to meet process and product requirements.

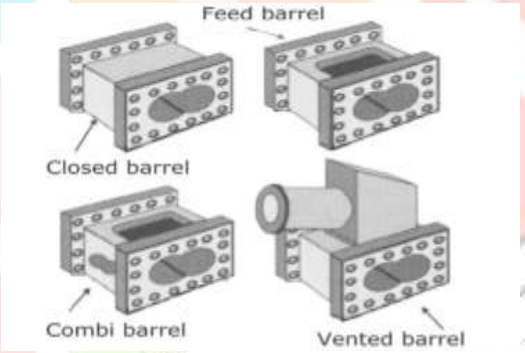


Figure 3. Barrel Types

Table no.1 : Barrel Types

Barrel type	Description
Closed barrel	Commonly used, liquid inject can be attached
Feed barrel	Circular or rectangular shaped opening on the top, the first section in extruder if required many can be placed as per requirement
Vented barrel	Used to remove air or volatiles from the extruder, has opened on top to connect vacuum or atmosphere

Being also a product contact part, the barrel material used in pharmaceutical HME has the same constraints regarding contamination and reaction with the melt stream as the screw elements.

For the housing for the screws to operate, the barrel construction should also offer some degree of flexibility to it should be possible for ports for material in-feed and venting to be placed anywhere along the barrel according to process requirements.

A segmented barrel approach is therefore widely used.

3.2 Screw elements

Screw design significantly impacts product characteristics and quality due to mechanical shear and residence time. One must design the screw depending upon materials as well as the process.

Screw configurations can be designed as shear intensive or shear passive depending on process requirements. The most widely used type is self-wiping, i.e., intermeshing corotating kind of screw design, but it is more concern about clearance and not actual mixing. Therefore, no one need not be constrained to classical screw types whose wiping may be excessive and demand unnecessarily high energy from the shaft.

Basic screw elements types

a. **Forwarding elements :** They are present at opening in the process, including barrel holes to forward the materials, at vent opening to maintain zero pressure, drain openings, and the discharge end of extruder pressurize the die. It helps in the forward movement of the material to the mixing zone.

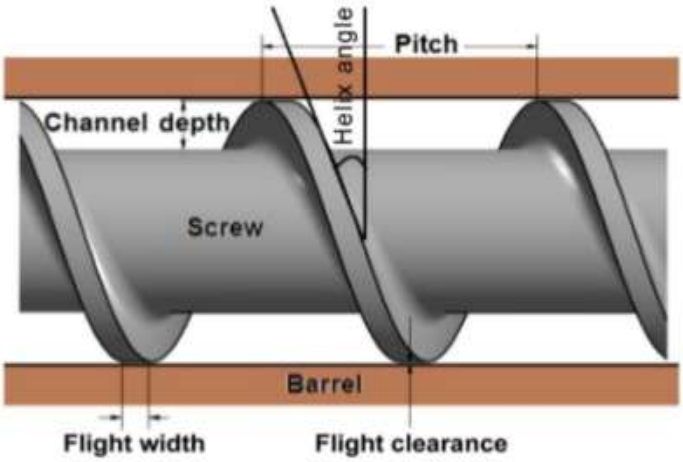


Figure 4 : Screw Configurations

In hot melt extrusion technology, the screw with a pitch less than one screw outer diameter is employed in the melt conveying section to generate pressure and pump the melt uniformly out to the die.

Table 2. Conveying screws design and impact on the process

Screw design	Free volume	Conveying efficiency	Pros	Cons
	+	+++	Low leakage flow High pumping efficiency	Lower conveying capacity
	++	++	Good balance between free volume and conveying efficiency	Higher shear than one-flighted screw
	+++	+	High conveying capacity	Some back-mixing

b) Mixing elements :

They can be either distributive or dispersive; distributive is a low shear process; it promotes homogeneity by diving and recombining the material without significantly reducing particle size. In contrast, dispersive mixing is a high shear process which involves particle size reduction as well as mixing.

Table no. 3 Types of mixing screw

Mixer screw type	Function
Reverse mixers	Push material backward and generates a large pressure drop
Neutral mixers	Push material neither upward or downward generates pressure
Forwarding mixers	Transport of material forward small pressure drop

Figure 5: Mixing screw

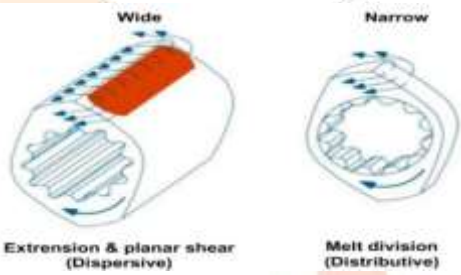


Figure 6. Narrow kneading disks provide proper distributive mixing, and wider kneading blocks provide dispersive mixing. \cite{Chen2017}

In hot melt extrusion technique, compression an decompression takes place, which leads to the elongation flow and dispersive mixing.

c) Zoning elements

They are elements that help in separating unit functions, e.g., to provide pressure seal for vacuum.
The function of zoning elements

1. Set boundaries for liquid inject
2. Blocks large particles to flow down and retain them so that proper mixing and melting take place.
3. Enhances the operation of mixing elements.

Reverse flighted elements, shearing discs, multisection neutral, or reverse kneading blocks are zoning elements.

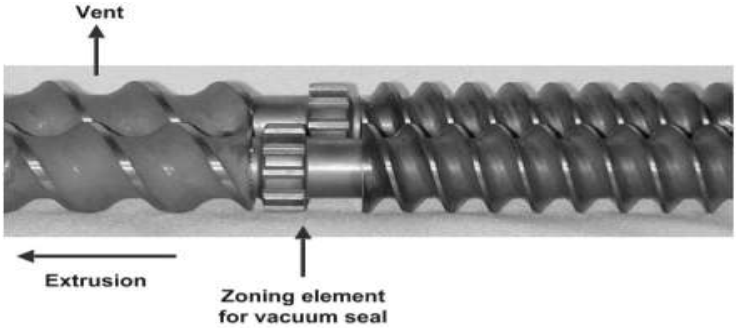


Figure 7: Zoning element

d) Special distributive mixing elements

They utilize interrupted screw flights to allow higher material exchange between adjacent screw channels, thus enhancing back mixing. {Chen2017}

Figure 8: Special distributive mixing elements.

Screw design engineering aspects

The ratio between screw length and screw diameter (L\D) is a crucial characteristic to consider, as it impacts the material residence time and the period assigned to each process operations. This ratio, too large extent, is determined by extruder design. This is the ratio of the length of the screw divided by the diameter. For instance, an extruder that is 100 mm long with a 2.5-mm screw diameter has L/D 40:1. Typical extrusion process lengths are in the 24:1 - 40:1 L/D range. Single screws have 36:1 L/D, or shorter. Intermeshing twin-screw extruders may configure for up to a 60:1 L/D. The non-intermeshing twin-screw extruder can be specified at 100:1 L/D or longer, due to the absence of intermeshing clearance is restricted. Residence times are generally between 10 sec to 10 min for any extruder. {Ghebre-Sellassie2003}

Other standard terms include an outside diameter of the screw (OD). For instance, when referring to a 40-mm extruder, this refers to the OD of the screw for a single-screw device or twin-screw machine both screws. The inside diameter (ID) is the OD less than the depth of the flight. The comparative OD/ID ratios will the free volume available in an extruder. There are also other different gaps in the extruder such as

a) Overflight gap: between the screw outer diameter and the barrel wall
b) Intermesh gap between two screws

An important design factor in any extruder is the channel or flight depth. Deeper channel depth increases the free volume in the machine. It must be recognized that a deeper flight depth in the feed zone area decreases the screw shaft cross-section and limits the possible torque transmittal. The proper balance between the free volume and torque must be maintained, as it will alter the throughput rate and mass transfer energy that is experienced by materials.

3.3 Dies

The final shape of the product is determined, and the intermediate products are further processed. Two main types of dies are generally mentioned in literature.

3.3.a. Flat die

Used for preparation of film or patches in which the thickness of the film may vary due to differences in the path of material in a central line and material at sides of the barrel walls. The middle layer had a compact structure than sides; to avoid these problems, bow shape dies design is used.

3.3.b. Annular dies.

Two major types of spiders die, and side fed die. Side fed dies are used if the coating is to be done because through such dies the material flows through the axis of die.

The material used in much pharmaceutical equipment is 316ss, but due to its soft nature, it is replaced with 420 or 17-4PH ss. They are harder and provide excellent strength. Capillary dies are made up of tungsten carbide.

3.3.c. Engineering aspect of the die.

- Thickness: Product thickness dependent on die design.
- Residence time: it depends on two main aspects

a) Mechanical aspect: Polishing of surfaces is necessary because if any cracks are present in the die, it may retain the material in that region, and thermal degradation of the material will take place, which leads to degraded material to each product exiting from the system.

b) Rheological aspect: Residence time depends on how the material flow in the system and is challenging to control.

c) Channeling is a concept developed when the channel is large for the required flow rate.
Pressure drop or resistance increase residence time. Pressure drop is the sum total of the shear stress over the entire flow channel, which means that the more is the shear stress, the higher the pressure drop through the systems. Die causes pressure drop which leads to the conversion of pressure drop into heat. This is called viscous dissipation or shear heating. The heat generated can be obtained using the following equation.

$$\Delta T = \frac{\Delta P}{\rho C_p}$$

Where T is the temperature rise, P is pressure drop, and rho is melt density, and Cp is heat capacity. Still, it is hard to calculate; engineers use software like FLOW 2000 CAE. The software helps to estimate the heat change in die.

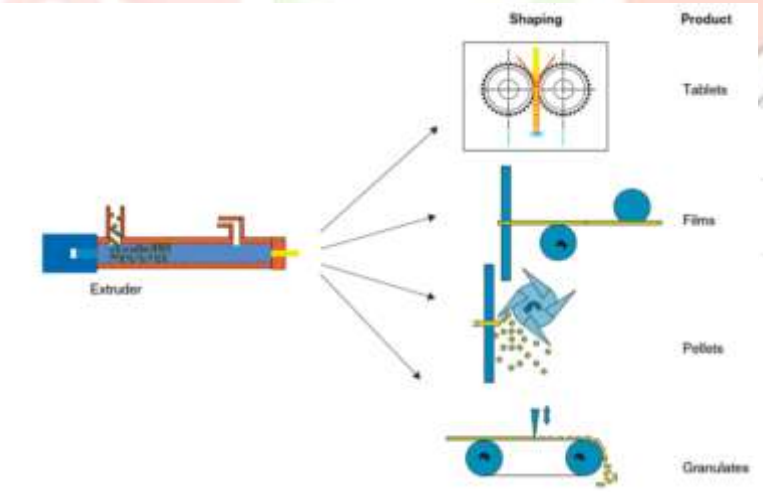


Figure 9 : Various types of dies used for the production of pharmaceutical products. Dies \cite

4. Processes design

Extrusion is a complex process that involves various unit operations. The process parameter plays a critical role in determining the quality of the end product. Throughout the extruder, the material, energy flow must be studied. The product quality is directly related to specific energy, melt temperature, residence time, and pressure. Indirectly affecting factors are adjustable like equipment parameters and process parameters.

4.1 Feed rate

In twin screw extruder counter-rotating type which is also known as drag flow pumps, in which conveying mechanism does not depends upon the material, same in counter-rotating extruders they are positive and conveying is independent of material characteristics.

a) Flood feed

The volume of material conveyed is directly proportional to the screw speed, the pitch, free volume. Screw speed determines the output rate in such systems. Analogous to the tablet press. In such an order, if one keeps the material and pace, constant output remains the same. Variations in raw material density, size cause surging. Not used for twin-screw.

b) Strave feed

The screw speed determines the output. Used for twin screw extruder mainly. In strave feed metering device, feed rate depends upon time material is delivered. Due to which the speed operates independently of output. Thus providing an additional degree of freedom for process capabilities, output depends upon precision and accuracy. Two main mechanisms are used volumetric fed and gravimetric feed. Screw feeders, vibratory feeders, belt feeders are used mainly. In which screw feed is widely used, constant speed gives constant volume.

The volumetric feed provides $\pm$ 2 % precision; in gravimetric feeders, the screw is only used with microprocessors placed, which check for a change in the weight, provides accuracy of $\pm$0.5 %. If the batch is blended initially and then added content uniformity would be maintained, even if minor segregation takes place. But in strave fed, the chances increase of change in content uniformity due to time-dependent flow. Back mixers can be used to tackle such a problem.

4.2 Melting

Two forms of energy are used in extruder: forced melting, dissipative mixing.

a) **Forced melting**: Provided with the means of electrical resistance heaters and thermal fluids. The rotation of the screw flight displaces the melt material, mixing the molten components into the bulk. This process depends on the thermodynamic properties of raw materials, particle size (and shape), percent fill of the extruder screw, and thermal gradient between the material and barrel surface.

The thermal contribution to melting can be quantified on a unit mass basis

$$specific\ thermal\ energy(kwh\backslash kg) = {thermal\ energy\ input(kwh\backslash hr)}\Big/{mass\ flow(kg\backslash hr)}$$

In extruder, surface area available for input volume is much more so the heat transfer is excellent than that of any other batch process. {Ghebre-Sellassie2003}

b) Dissipative melting

Extruder energy is converted into heat energy, due to viscous dissipation. Melting occurs as solids are confined to decrease clearances. Screw-type extruders are designed to convert electrical energy from the drive motor into mechanical energy via viscous dissipation. Melting occurs as solids are confined to decreased clearances (twin-screw extruders) and/or decreased free volume (single-screw extruders). In co-rotating twin-screw extruders, staggered kneading discs are employed to melt materials. Melting typically occurs rapidly within several kneading discs in a twin-screw extruder and over several diameters in the compression section of single-screw extruders. This melting mechanism is directly influenced by mechanical energy input from the drive motor and can be quantified on a unit mass basis:

$$specific\ mechanical\ energy(\text{kwh\kg}) = \frac{consumed\ motor\ power\ (kwh\backslash hr)}{mass\ flow(\ kg\backslash hr)}$$

The thermodynamic properties like temperature and particle size are all critical parameters contributing to the efficiency of the extruder during viscous- dissipation.

Additives like lubricants and materials with low melt viscosity can adversely affect the mechanical energy input and, indirectly the melting process. Rarely any material is melted using only one mechanism. Materials generally require both thermal and mechanical contributions to achieve a complete melting. For thermoplastic materials energy input range is between 0.1 and 0.4 kwh\kg. Specific thermal energy input is always less than that of the Specific mechanical energy. It is suggested that the material must be injected in the decreasing order of the melting point so that low melting substances are not exposed more to the heat and degrade. This second component would melt rapidly at the higher temperature and would also have less residence time. Polymers that melt at relatively low temperatures, for example, waxes, may prematurely melt in the feed opening of the extruder barrel, causing problems with feeding. In these cases, the feed barrel is kept cool with increasing temperature in the subsequent barrel modules.

4.3 Mixing

a) Dispersive mixing

Screw-type extruders produce a fluid shear stress as a result of the velocity gradient of rotating screw(s) and a stationary barrel. It is this shear stress that is responsible for reducing the size of the drug , also referred to as dispersion or dispersive mixing. In a simplified form, the magnitude of the applied stress is a function of the shear rate and the melt viscosity:

$$shear\ rate\ (sec^{-2}) = \frac{[\pi \times screw\ diameter(mm) \times screw\ speed\ (rpm)]}{[gap(mm) \times 60(sec\backslash min)}$$

where the gap is defined as the distance between the moving surfaces (e.g., the mechanical clearance between screw and barrel or between screw/screw in twin-screw extruders).{Ghebre-Sellassie2003}

The range of shear rate achievable in screw extruders is between 10 and 10,000 sec^{-1}. High values of shear rate are achieved with large screw diameter, high screw speed, or small gap. Thus, for a specific extruder diameter operating at a specific screw speed, the highest shear stress occurs where the viscosity is the highest, i.e., during the initial melting of polymer(s). This concept motivates us to feed all components into the first feed opening of the extruder to provide the highest degree of dispersive mixing. Conversely, the thermo-sensitive compounds are fed downstream to avoid the thermal degradation of the compounds. Due to this the shear stress experienced by the thermosensitive compounds is much lower. This shear stress causes a decrease in minor phase size, also referred to as morphology development. The final stage is a frozen stage in which the polymers are cooled below their glass transition temperature after they come out of the extruder die. The resulting morphology is responsible for producing a particular dissolution profile or bioavailability. The extrusion parameters that influence shear stress are used to control the morphology (i.e., dispersive mixing). These parameters listed in order of significance:

1. Screw design: The configuration of the screw (including overall L/D and mechanical clearances) will determine how much of the material will experience high shear stress. Flow-restriction devices are used in twin-screw extruders to force the material through small clearances.

2. Screw speed: it is directly proportional to the shear rate. The direct effect is produced by screw speed in flood feeding, and nonlinear effect is shown by twin screw extruders, which are generally strave feeded (because increasing screw speed at a constant feed rate will also produce a decrease in the filled screw volume).
3. Feed rate: Directly proportional to shear rate for flood-fed extruders, because the only way to increase feed rate is to increase screw speed. The effect of increased feed rate on starve-fed extruders is to decrease the ‘‘effective’’ shear rate because the filled screw volume will increase at a constant screw speed. The increase in filled screw volume means that more material is occupying that portion of the screw channel with larger gap (i.e., in the center of the screw channel), as opposed to when the screw is nearly empty when most of the material is occupying that portion of the screw channel with smaller gaps (i.e., clearance between screw and barrel).
4. 4. Barrel temperature. Increasing barrel temperatures will decrease melt viscosity, thereby decreasing the shear stress.

b) Distributive Mixing

Distributive mixing can also be viewed as homogenization, where the concentration of the minor phase (e.g., active compound) is constant throughout the volume. Distributive mixing is responsible for the content uniformity of a particular constituent, whereas dispersive mixing is responsible for the size and distribution of a constituent. Distributive mixing is achieved in an extruder by the interchange of discrete volumes contained within the extruder screw. Twin-screw extruders contain multiple screw channels (i.e., discrete volumes), which can be split and recombined. Screw elements are available for twin-screw extruders, which promote distributive mixing by modifying the number of discrete volumes; single-screw extruders contain only one screw channel and therefore rely on interruptions in the flow channel to provide reorientation.

4.4 Venting

Volatile compounds present must be removed from the extruder. Venting depends on the melting temperature, vacuum level, and residence time under vacuum. The screw in the vent area must be designed such that a large surface area is provided. The upstream and downstream must be completely filled in order to sustain the vacuum in the system properly. The die acts as a vacuum seal downstream, and restrictive screw elements must be used to seal upstream. Vacuum levels of less than 100 bar easily achieved.

4.5 Die pressurization

The extruder must generate the pressure that overcomes the resistance developed by the dies. Pressure drop can be calculated for simple shapes provided that we know the viscosity and flow rate of material in us. Large die face problems which lead to non-uniformity in flow rate.

For continuous operation die pressure required is generally, in range of 200 to 350 bar. Due to die pressurization, melt temperature increases due to viscous dissipation. Some may use gear pumps to overcome problems related to flow rate and die pressure.

4.6 Processes length

The length of the extruder is determined by the input operations that are to be carried out during the extrusion technique. Twin-screw extruder barrel modules are designed sich as equal or four times the screw diameter. Limitations over the length are due to the torque generated.

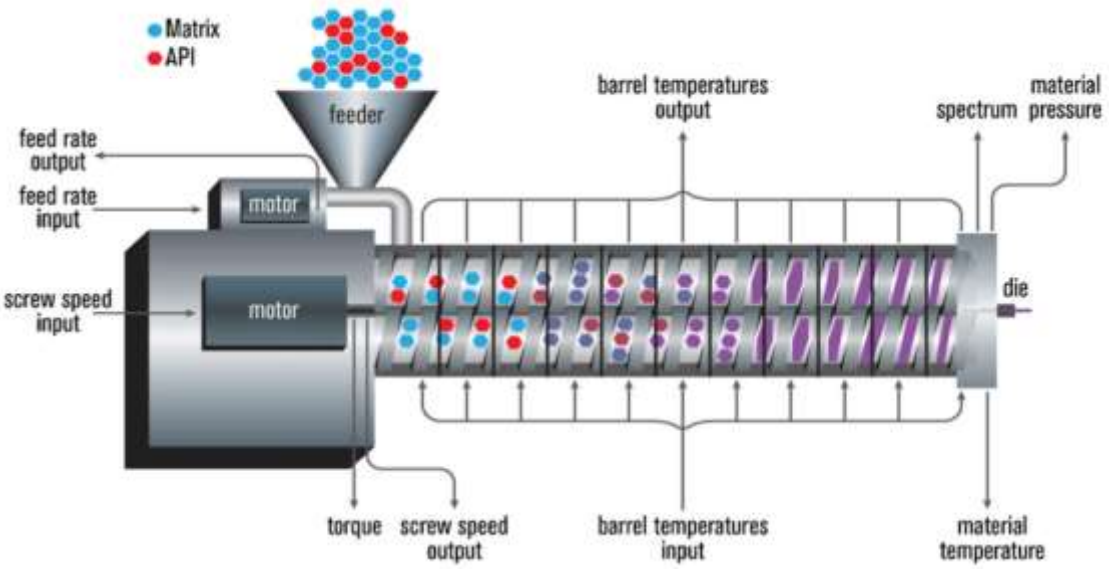


Figure 10: Hot Melt Extrusion Process

5. Hot-melt extrusion technique

HME evolving as a new platform technology for the manufacturing of solid dosage forms. The number of patents based on hot-melt extrusion technology is day by day increasing. In the hot-melt extrusion process, the thermoplastic polymers are used, which act as a carrier for the drug substance. Other excipients like plasticizer, diluent, antioxidants, preservatives, release modifiers are used.

Advantages of hot-melt extrusion technique over the conventional process

1) Solvent-free technology
2) Continuous processing
3) Do not require significant downstream processing.

Disadvantages

1) Thermolabile drugs cannot be processed using HME**.**

Table no. 3: Formulations in the market manufactured using hot-melt extrusion technique.

Pharmaceutical form	Commercial name	Owner	Drug(s)	Therapeutic indication	HME purpose
Ophthalmic inserts	Lacrisert®	Merck	-	Dry eye syndrome	Shapes rod
	Ozurdex®	Allergen	dexamethasone	Macular edema	Shape
Implants	Zoladex®	Asra Zeneca	Goserilin	LHRH agonist	shape
	Depot – profact ®	Sanofi Aventis	Buserelin	Carcinoma of the	shape

				prostate gland	
	Probuphine ®	Titan	buprenorphine	Opiod dependence	shape
devices	Mplanon®	Schering-plough	Etonorgestrol	contraceptive	shape
	Nuvaring ®	Nv organon	etonorgestrol	contraceptive	shape
	Annovera®	Therapeutics MD	ethynylestradiol	contraceptive	shape
Oral	Kaletra	Abbot	Lopinavir	HIV	Amorphous solid dispersion
	Isoptin®	Abbot	Verapamil	Hypertension	Shape
	Covera®	Pfizer	Verapamil	Hypertension	Melt granulation
	Nurofen®	Reckitt benkiser	Ibuprofen	Analgesic	Melt granulation
	Novir ®	Abbot	Ritonavir	Peg glyceride	Amorphous solid dispersion
	Gris-PEG®	Penidol	Gresiofulvin	Onychomycosis	Crystalline dispersion
	Rezulin®	Parke davis	Triglitazone	Diabetis	Amorphous solid Dispersion
	Cesamet®	Meda pharmaceuticals	Nabilone	Antihelmentic	solid dispersion
	Adalat®	Bayer	Nifedipine	Antianginal	Controlled release
	Eucres®	Novartis	Vildgliptin	Disbetis type 2	Melt granulation
	Zythromax®	Pfizer	Azithromycin	Antibiotic	Melt granulation
	fenoglide®	Lifecycle pharma	Fenofibrate	Dylipidemia	Solid dispersion
	Noxafil ®	Merck	Posoconazole	Antifungal	Amorphous solid dispersion
	Onmel®	Merz	Itraconazole	Onychomycosis	Amorphous solid dispersion
	Palladone®	Purdue pharma	Hydromorphone	Pain relief	Controlled release
	nucynta®	Janseen	Tapentadol	Pain relief	Controlled release
	Opana ER®	Endo pharmaceutical	Oxymorphone	Pain relief	Controlled release
	belsomara®	Merck	Suvorexant	Hepatitis C virus	Amorphous solid dispersions
	Technivie ®\Viekirax®	Abbvie	Ombitasavir	Hepatits C virus	Amorphous solid dispersions

	Virkira	Abbvie	Ombitasvir, paritaprevir, ritonavir	Hepatitits C virus	Amorphous solid dispersion
	Venclyxto ®	Abbvie	Venetoclax	Chronic lymphocytic lrukrmia	Amorphous solid dispersions
	Maviret®	Abbvie	Glecaprevir/ pibrentasvir	Hepatitis C virus	Amorphous solid dispersion

6. Product development

6.1 Polymer selection

A most crucial parameter in polymer selection for hot melt extrusion is the solubility of polymer and drug in each other. Various approaches which are mentioned in literature like Garden Taylor equation, Flory Huggins equation, calculation of Hassens parameter, developing constructional phase diagram. {Simoes2019b},Marsac2009}

- Miscibility

a) Garden Tylor equation
   - Prediction of Tg of the blend measure positive or negative deviations from real Tg.
   - Easy to use
   - It provides limited information
   - For example, the equation was applied and the impact of the molecular structure of sorafenib and its fluorinated compound regorafenib, positive change in the Tg was seen and confirmed using NMR spectroscopy.

b) Flory Huggins equation
   - Usually, based on melting point depression theory, if the compound ids miscible then melting point depression will take place.
   - It considers specific intermolecular interactions
   - Requires DSC
   - High accuracy in the high drug loading, which is rarely the case of amorphous solid dispersions

c) Hansen solubility parameter
   - Usually based on GC method
   - Compounds with similar values are expected to be miscible
   - Generally, a good correlation is observed
   - Low predictability of systems showing strong interactions
   - The total Hansen solubility parameter ðt for drug, polymers is calculated based on partial solubility parameters

$$ð = \sqrt{(ð^2\,drug + ð^2 polymer)}$$

variables ð drug, ð polymer refers to the molecular densities of energies that resulted from dispersion, polar, and hydrogen interactions respectively.

d) Computational methods

Mathematical calculations is done for entered data

Thermal analysis

a) Differential Scanning Calorimetry Analysis
b) Hot stage microscopy
c) Melt flow index
d) X-ray diffraction spectroscopy

Examples of polymers used in hot melt extrusion technique

- **Immediate release**

Polyethylene oxide (PEO)
Polyethylene glycol (PEG)
Polyvinylpyrrolidone (PVP)
Hydroxypropyl methyl cellulose (HPMC)
Hydroxypropyl cellulose (HPC)
Vinylpyrrolidone/vinylacetate copolymer (KollidonR VA)
Dimethylaminoethyl methacrylate copolymer (EudragitR E)
PEG 6000 / vinylcaprolactam / vinylacetate copolymer (SoluplusR)

- **Sustained release**

Ethylcellulose (EC)
Ethylene vinyl acetate (EVA),
Polyvinyl acetate (PVA)
Poly(L-lactic acid) (PLA)
Poly(lactic-co-glycolic acid) (PLGA)
Polycaprolactone Silicone Ammonium methacrylate copolymer (EudragitRS/RL) Lipid matrices (microcrystalline wax, stearic acid, carnauba wax, etc.) {Kachrimanis2015}

6.2 Active pharmaceutical ingredients

Crystalline drug are manufactured and preferred in chemical industries due to the physical and chemical stability of the drug in crystalline form. Even though the crystalline products are thermodynamically stable, it important to know the polymorphic changes that take place during the hot-melt extrusion process.

The biggest drawback of the crystalline product is that it has poor dissolution; pharma industries prefer to use the amorphous form of the drug.

However, amorphous products are thermodynamically unstable. The process of devitrification very commonly occurs with amorphous products and causes them to convert to the crystalline form, following storage. Therefore, the glass transition temperature (Tg) monitoring is essential for amorphous products. Tg should be at least 50°C above the storage temperature to ensure product stability. In addition to exhibiting thermal degradation, the active ingredient may enhance or interfere with the functionality of the other components in the formulation.

6.3 Plasticizer and surfactant selection

The addition of a plasticizer to facilitate the melt extrusion process is well established in the plastics and pharmaceutical industries. Plasticizers can lower the glass transition temperature and the melt viscosity of the polymer. Surfactants such as sorbitan monolaurate and tocopherol are present in Amorphous solid dispersion of several commercial products. These surfactants are present to modify the precipitation and crystallization behavior of ASDs in an aqueous environment. The primary concern with using the traditional plasticizers is that the ASDs' physical stability might Scale-up during the storage because of the lower glass transition temperature. A transient plasticizer is intimately mixed with the polymer melt inside the twin-screw extruder and subsequently removed completely from the extruded product upon exiting the die. Supercritical CO2, a blowing agent commonly used in plastics industry, is an ideal transient plasticizer for pharmaceutical melt extrusion

7. Scale-up process for twin-screw extrusion

Hot-Melt-Extrusion on Twin-Screw-Extruders has been established as a standard production technology in pharmaceuticals industry. A major challenge is the scale-up from a lab to a manufacturing level. Since the combination of several unit operations within equipment leads to complex conditions for such a continuous manufacturing process. Here the residence time distribution is a crucial measure, which reflects the different mechanisms, e.g., dissolution, mixing, or degradation, during processing.

The parameters that are affecting the scale-up is handled differently in each case, keeping all other criteria constant. Basic case is that the scaling up of the basis of the geometry of the screw, L/D, diameter, and design.

When the process depends on the power the torque generated is considered and mathematical calculations are done to determine the required power.

When factors like residence time, heat flow is a hurdle in the scale-up then one must go for heat transfer scale-up.

Simulation assisted scale-up strategy is now coming up, it will ease the process understanding of HME, software like Ludovuic are used in the plastic industry now they have been modified for pharmaceuticals. More focus will be given on the simulation assisted scale as it is the future of the hot-melt extrusion scale-up plan.

Extruder scale-up can be done in following three cases

Case 1: Increasing production output on a HME process by increasing the batch size (using the same extruder and or multiple extruders of the same size).

Case2: Increasing production output on a HME process by increasing the feed rate (with or without changes to other process parameters) on the same extruder.

Case 3: Increasing production output on a HME process by increasing the feed rate (with or without changes to other process parameters) on a different extruder with larger dimensions.

7.1 The batch size scale-up

As twin-screw extruders are continuous types of processing equipment, the only time of the operation is to be increased. In general, the manufacturing batch record is also the same. Only the extent of time is changed. Keeping all of the parameters, the same one can ensure the product quality.

7.2 Feed rate scale-up

It may happen, so for an established product, the feed rate has to be increased to enhance production capacity. An increase in the feed rate directly impacts the residence time of material in the extruder causing the thermal changes in polymer and drug substance processing. The only possibility of maintaining an average residence time constant at two different feed rates would be to extend the length (i.e., free volume) of the TSE together with feed rate, although this is not a practical solution.

7.3 Geometric scale-up

a) Length \ diameter ratio :

The ratio screw barrel length and screw diameter, and length of each processing section are essential for a unit operation like mixing, melting and conveying. This ratio, to a great extent, is determined by screw design. For example, the diameter for the lab-scale extruder is 20mm, and the length is 800 mm, then for scaling up the extruder of 40mm diameter, the length must be 1600mm. Both of them will give the same L\D value.

b) Screw diameter ratio :

D outside and Dinside are the ratios of diameters of the screw. This ratio impacts the shear stress that the material experience, less the ratio more is the shear and vice-versa. This ratio also impacts the free volume present in the system. Generally, it changes from manufacture to manufacture. Most twin-screw extruders marketed have a ratio of 1.45 and 1.75.

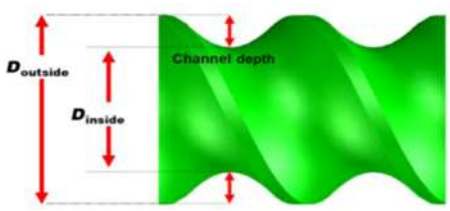


Figure 11: Screw

7.4 Volumetric scale :

It is considered when the free volume limits the throughput. An increase in the throughput by increasing the screw speed can also be done. When we considered the two extruders are geometrically similar, the shear rate, degree of fill is also expected to be reproducible.

Case 1 When the same screw diameter ratio, the same shear rate is expected when operating at the same screw speed. The volumetric scale-up is believed to follow the cubic law

$$Q_2 = Q_1 \left(\frac{D_2}{D_1}\right) 3$$

Where Q_2 is anticipated throughput of the extruder with a diameter D_2, Q_1 is measured throughput of the extrudate with a diameter D_1.

Case 2 When the screw diameter ratio is different between extruder, but similar screw geometry with same speed formula can also be modified to,

$$Q_2 = Q_1 \left(\frac{\boldsymbol{FREE\ VOLUME\ 2}}{\boldsymbol{FREE\ VOLUME\ 1}}\right)$$

As the residence time depicts mass flow patterns in the extruder, it is essential to obtain that information during the scaling process. Tracers can be added inside the system, and depending on it, the residence time is measured figure given below.

Figure 12: residence time measurement using tracers. ("LR71-e-Investigating-Process-Parameter-Mechanism Thermo-Fischer)

7.5 Power scale-up

Specific energy provided must always be constant for scaling up the process. Maintaining constant energy is important because the energy input is essential to achieve the desired product quality. Specific energy applied is a total of specific mechanical as well as specific thermal energy.

$$specific\ mechanical\ energy = \frac{power}{throughput}$$

The premise of applying this calculation during scaling is similar to screw geometry, the same percentage of fill, and equivalent screw speed as measured by tip velocity. The maximum throughput can be calculated with a given SME for the small extruder and available power for the large extruder.

When we compare the throughput using a volumetric scale-up strategy, a disparity may be observed. This could be due to the torque density difference among extruders. Torque density describes the relationship between power and free volume.

$$torque\ density = torque\backslash centreline\ distance$$

When scaling up with lower torque density using a power scale-up strategy and not considering torque density, the calculated output may be less than a volumetric scale-up strategy. The false output may due to the process operating at a lower degree of fill, higher shear rate, and longer residence time. Thus, the torque density should be assessed before the application of the power scale-up strategy.

SME is a function of torque, screw speed, and throughput in which screw speed and throughput are adjustable process parameters, while torque is a response variable. Thus, this strategy can also be used to evaluate the relationship between power (as a function of torque and screw speed) and screw speed. In general, if an increase in throughput is desired, screw speed should be increased congruent to maintaining constant SME.

7.6 Heat scale-up

When the scale-up is limited to heat transfer, one must go with a heat transfer strategy. The factors affecting heat transfer, such as barrel surface area, the temperature gradient between barrel surface and processing material, residence time.

When the degree of fill and screw diameters are constant, the following equation is used during heat transfer scale up….

$$Q_2 = Q_1 \left(\frac{D_2}{D_1}\right) 2$$

Generally, heat transfer limit is not common in pharma, but when we use large extruder, the heat transfer between material per unit mass get reduced. Thus, while scaling using heat transfer strategy one must operate large extruders at a low feed rate. {Ghebre-Sellassie2003}

7.7 Simulation strategies for scale

Extrusion simulation allows for process scale-up with high confidence and in a cost-efficient manner. Simulation-assisted scale-up is particularly useful when geometric similarity and the requirement for classic scale-up strategies cannot be met. The ultimate goal of simulation tools is to produce a glass extruder so that the process is fully understood, and all properties are visible. Based on the number of spatial model dimensions, modeling approaches can be categorized into:

(1) (0-D), Zero-dimensional models, which focus on the balance of the complete extruder or an individual section;

(20 1-D, one-dimensional studies, which focus on the process along the extruder axis;

(3) (2-D, 3-D), two- or three-dimensional models, which consider the cross-section and require defined the boundary condition to reflect the process better.

The 3-D models, typically based on complete numerical solutions of motion equations using FEA or similar techniques, provide an accurate and detailed picture of the flow field during the extrusion process.

Polyflow is a commercially available 3-D simulation software. This model assumes a fully filled extruder under nonisothermal conditions and can track the simulated movement of particles. The software output is a 3-D description of flow in an extruder, including distributions of temperature, pressure, shear rate, and other responses. Additionally, the software can quantify dispersive and distributive mixing as well as predict stagnation areas. However, since this model can only simulate the viscous fluid-filled zone, it is not possible to model an entire extrusion process along the length of the screw.

Ludovic is the most widely used in the pharmaceutical industry. Although different 1-D models can be developed based on different theories and/or calculation methods, the typical simulation outputs include temperature, pressure, fill ratio, viscosity, shear rate, energy consumption, and residence time distribution The emphasis on the change along the screw axially for particularly challenging to measure system parameters (i.e., energy distribution, residence time distribution, and material temperature) enables thorough process understanding and easy process scale-up. It was reported that computational extrusion process simulation using Luduvic could identify high energy intake locations and allow optimization of screw design to ensure scalability.

✓ **LUDOVIC**

Virtual extrusion lab, Ludovic reproduces extrusion processes like screw geometry, material, and operating conditions.

- Ludovic 4 TAB technology

During simulation three, fundamental input data are considered extruder, products, process, and the execution, and steps provide a path for twin screw extruder simulation.

❖ **Extruder tab**
Shows various extruder geometry ---modify—model screw geometry, feeding zone, die.

❖ **Product tab**
Can import materials from various databases.

❖ **Process tab**
Define operating conditions

❖ **Execution tab**
To run a simulation.

a) Energy consumption of process : Total conduction energy + dissipation energy+ specific energy is given and sown as output in percent.

b) Design of experiment : To determine product and process suitability, we can test various conditions and compute the data. The software will give complete function domain, and then we can develop boundaries to our domains.

c) Screw profile : Results along the screw profile are shown; the plots of various screw profiles and different results can be plotted as shown in the figure.

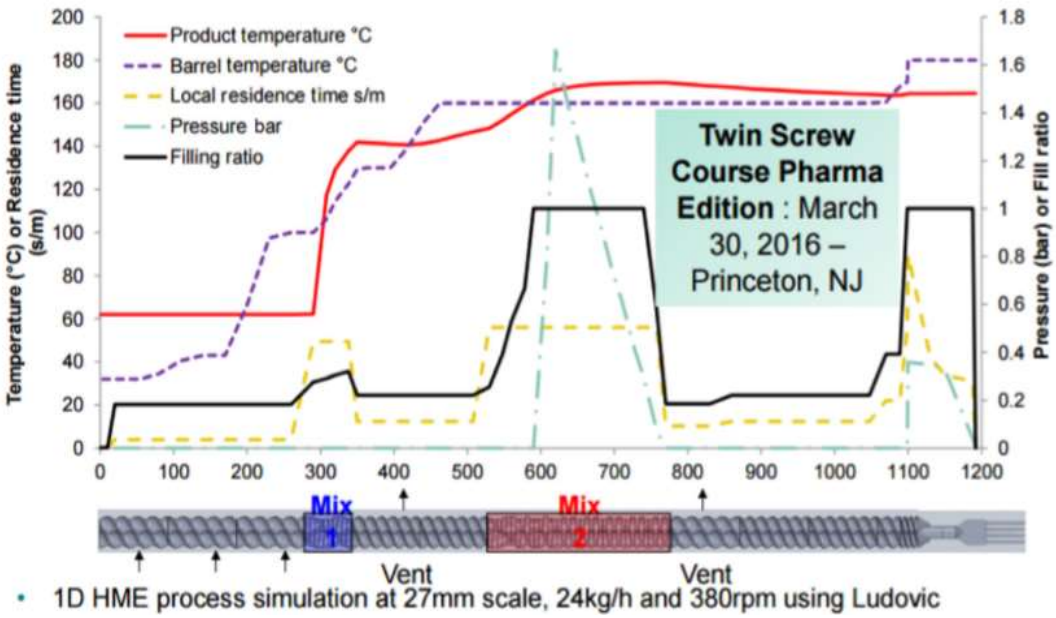


Figure 13: Modeling of hot melt extrusion.

8. Quality by design approach to hot-melt extrusion technology

Quality by design provides a systemic approach for the development of the dosage form. The development approach depends on the quality risk management process. Once the quality target product profile is determined, which is linked with safety and efficacy. {Evans2019a}

Critical process parameters

The extrusion process can be divided into the following steps{Islam2014}

a) Feeding of the material in the extruder.
b) Conveying and mixing of the material with the help of screw
c) The flow of melted mass from die
d) Exit from die and shaping

The following figure shows the Critical process parameter

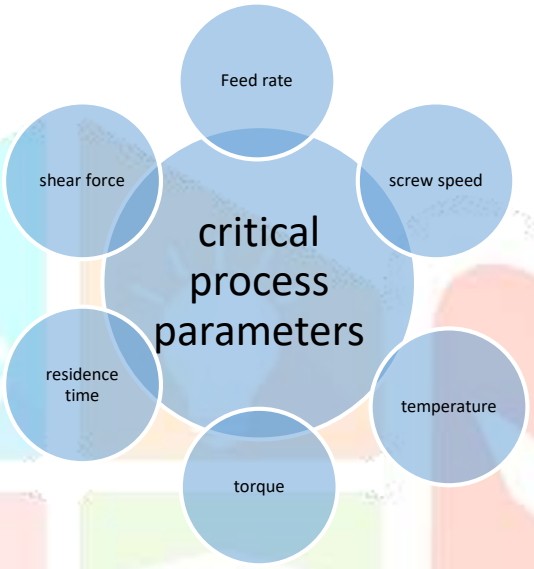


Figure14: Critical process parameter

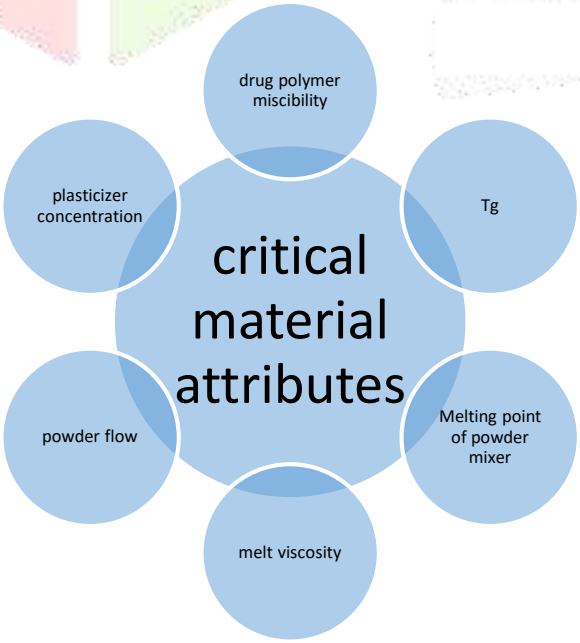


Figure 15 : Critical material attributes

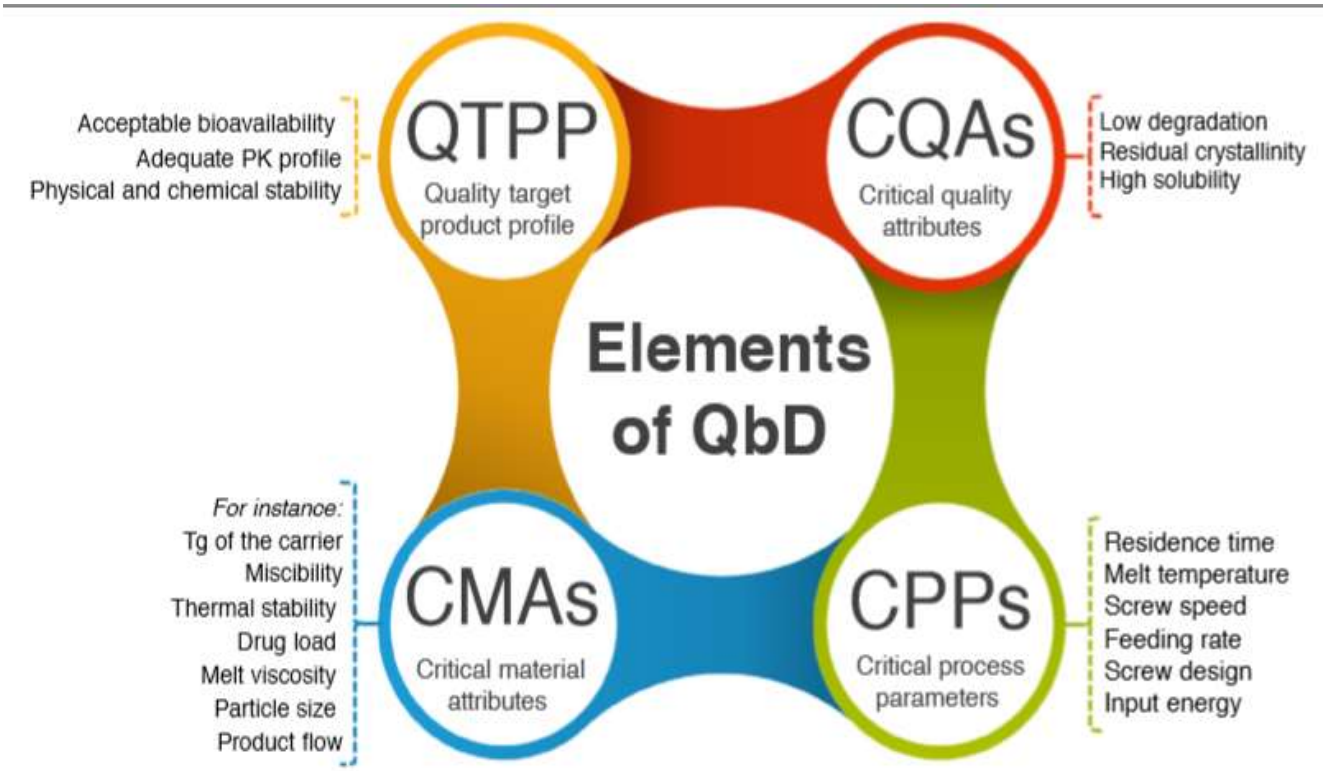


Figure 16: **Quality by design approach for hot-melt extrusion.**

The quality risk analysis tools like the fishbone diagram of FMEA are used.

In the failure mode effect analysis, the threat containing parameters are only highlighted. FMEA, the stepwise approach, is used to modify the process so that future failures are prevented. The results are reported in the form of a risk priority number. The failure mode is recorded on the scale of 1-5, with respect to severity(S), occurrence (O), detectability (d)

Risk priority number = S × D× O

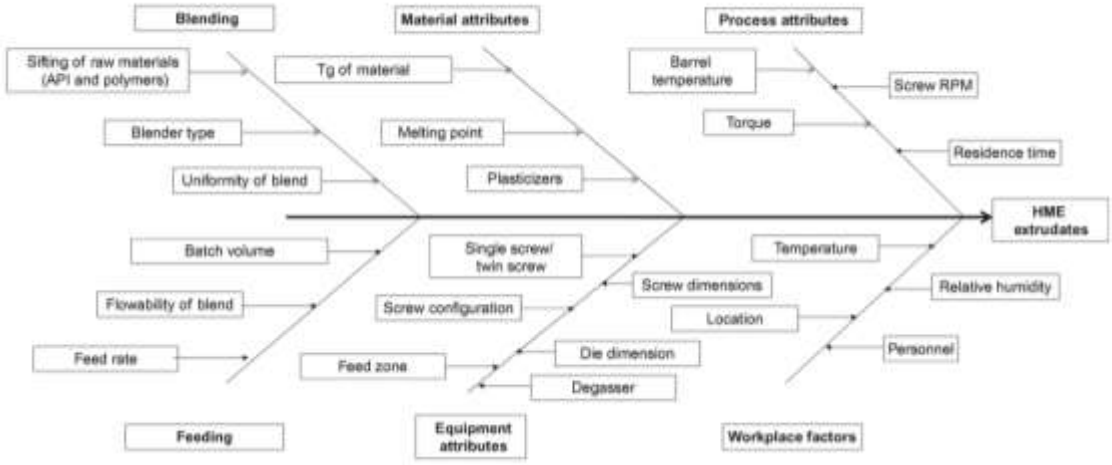


Figure 17: Ishikiwa\ Fish Bone Diagram

9. PROCESS ANALYTICAL TECHNOLOGY

Another critical component of quality by design is process analytical technology. The implementation of the process analytical technique provides various benefits like

- Lower production cycle times
- Improved manufacturing efficiency
- Reduction in rejection batches
- Increased production operating time.
- There is no need for the sampling to detect the ongoing process.

Hot melt extrusion technology evolving is field due to its potential to solubilized poorly soluble drugs when formulated in the form of the amorphous solid dispersions. In amorphous solids dispersions, drug may be converted into crystalline form, that may lead to variations in drug release to monitor this conversion and validate the process PAT system have been adopted by many industries. Many known analytical techniques like NIR, Raman spectroscopy, UV spectroscopy, tetrahertz, and ultrasonic are used this days.

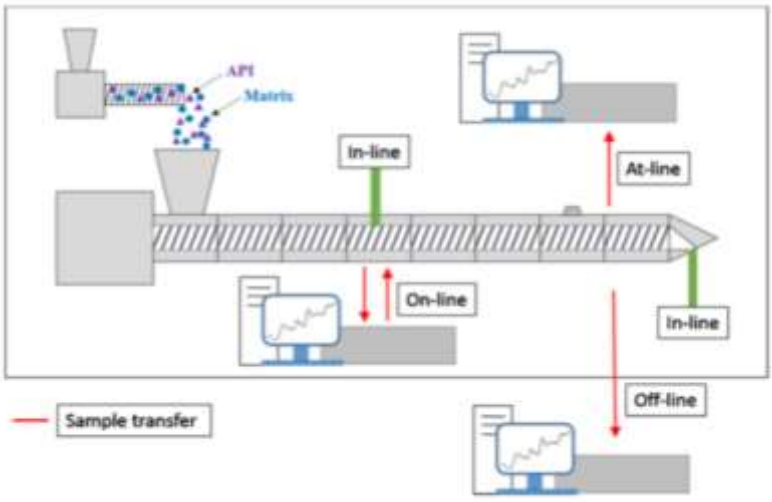


Figure 18: In-line, Online and At-line process monitoring

9.1 NEAR infrared spectroscopy

- NIR spectroscopic region falls between 4000 to 12000 cm-1; the peak are broad in comparison to that of the IR spectroscopy.
- Overtone peaks of –SH, OH, -NH bonds are detected but are not interpretable without chemometric analysis. Beyond this drawback, NIR has various advantages.
- Nondestructive, fast, continuous, noninvasive.
- Additionally, NIR spectroscopy is sensitive to changes in hydrogen bonding and rearrangements in the crystal lattice, which grants the possibility of understanding molecular interactions
- The relationship between spectral data and known properties of the samples must be established from standard spectra either by collecting light reflected off a sample (reflection) or light transmitted through a sample (transmission).
- The opaque nature of polymer and drug would lead to wrong interpretations, for such samples transmission principle is used.
- Quantification requires a calibration model to be developed with the accuracy of the model tied to the accuracy of a primary quantitative analytical method (e.g.HPLC).
- For qualification analysis, spectra of standards with known classes are used to develop a qualification model.

- For identification analysis, spectra of known chemical identification are used as standards for identification model development.
- For all three analysis types in the pharmaceutical industry, the calibration model must be validated before it being put into use for QA/QC testing. {Hitzer2017}

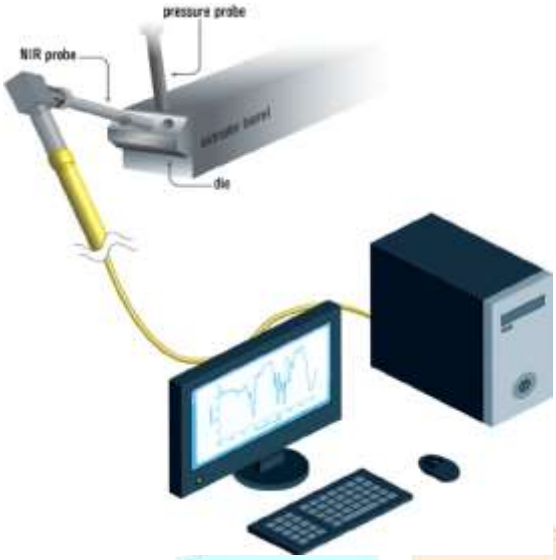


Figure 19: NIR PAT system

Figure 20: Dysino NIR probe

9.2 MIR

- Holds the same advantages as that of the NIR but due to low penetration depth. The study on MIR spectroscopy is much less than NIR.
- It helps in determining the in-situ polymerization in extruder itself.
- Research in this field is much limited.

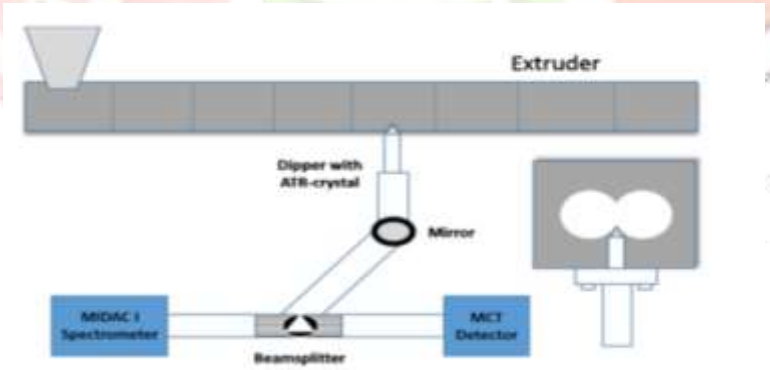


Figure 21: ATR MIR PAT system

9.3 Raman spectroscopy

When molecules are irradiated with IR source, the scattered radiation is of the same wavelength as irradiated once. These scattered radiations are called Rayleigh scattering occurred due to elastic collisions. Stokes and anti-stokes scattering occurs at low intensity. Elastic collisions keep the energy of a molecule unchanged, inelastic collisions excite vibrations and rotations that emanate from either the ground state of the molecule (Stokes Raman scattering) or from an already excited state of the molecule (anti-Stokes Raman scattering). Because most molecules appear in their ground state, it is usually only the Stokes spectrum that is measured. During this kind of molecule excitation, there is a loss of energy, which exactly matches the amount of energy necessary to excite vibrations and rotations of that molecule. The difference between the frequency of the

irradiated light and the frequency of the Raman scattering matches the frequency of the absorption bands in the spectrum. {Tahir2019}

- Used to determine drug concentration, polymer-drug interaction, and also determines the impact of processing parameters during scaling up.

9.4 UV spectroscopy

Mainly used in the food and plastic industry for extrusion process monitoring, in pharmaceutical extrusion, it can give information about color change occurred in the material during processing.

9.5 Terahertz spectroscopy

- Tera hertz region falls between the 30micron and 3000micron range between infrared and microwave regions in the spectrum.
- The terahertz spectroscopy determines lattice vibration and weak hydrogen bonding, thus helps in the determination of polymorphs.
- Crystallinity determination is more accurate than MIR and NIR spectroscopy.
- However, still not fully developed as a PAT tool.

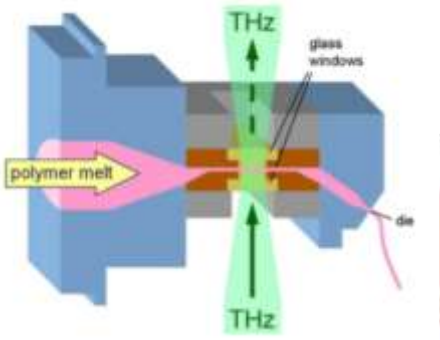


Figure 22: Extrusion die: the terahertz beam propagates through the polymer that is enclosed by two quartz glass windows.

9.6 Ultrasound spectroscopy

Monitor and measure critical parameters such as particle size distribution (PSD), crystal size distribution (CSD), and crystal growth during the crystallization process.

10. CASE STUDY 1

10.1. Opioid extended-release tablets with improved tamper-resistant properties.(Bartholomaeus et al., 2012)

Many pharmaceutical companies have tried using various approaches for developing abuse-resistant dosage form.

Suggested approach

1. Embeda (morphine sulfate controlled-release/naltrexone) includes a sequestered opioid antagonist that is released if the product granules are crushed, neutralizing opioid effects.
2. Oxecta (oxycodone; King Pharmaceuticals Inc., Bristol, TN, USA), an immediate-release, includes nonsequestered aversive excipients that cause mucosal irritation if the product is abused via inhalation and exhibit gelling properties that deter injection.
3. Nucynta ER (tapentadol ER; Janssen Pharmaceuticals, Inc., Titusville, NJ, USA), reformulated OPANA ER (oxymorphone ER; Endo Pharmaceuticals Inc., ChaddsFord, PA, USA)and reformulated

OxyContin(oxycodone CR; Purdue Pharma L.P., Stamford, CT, USA) incorporate physical barriers to crushing and form a viscous gel upon dissolution in fluids.

But still the above systems have some sort of disadvantage, Some patients which unintentionally crush or try to dissolve a tablet with no intent of abuse, will lead to pill phobia, dysphagia, and partial dosing.

One of the successful formulation strategies to deter this abuse is to prepare a dosage form with high physical strength to prevent crush and extraction. Both Poly (ethylene oxide) is used as the drug-release retardant and matrix former. The manufacturing process consists of blending, extrusion, cooling, cutting, forming, and coating. During the melt extrusion, the poly (ethylene oxide) based matrix formulation is melted and pressurized. As a result, the melt-extruded matrix possesses strong physical strength in comparison to the tablets prepared using a conventional tableting process. The resulting PEO matrix tablet exhibits a breaking strength of greater than **500 N**.

CASE STUDY 2

Solubility enhancement of drugs using Hot melt extrusion techniques

Rezulin is the first marketed product containing Amorphous solid dispersion manufactured using the HME process. Troglitazone, is a BCS class II drug, the active component of Rezulin, with low and highly variable bioavailability. At the time of the product approval in the 1990s, Parke-Davis/Warner-Lambert had already developed an organic solvent-based spray-drying process to prepare a povidone-based ASD of troglitazone with enhanced bioavailability. But due to high cost, safety, the environmental impact of organic solvents concern arose. An effort to identify an alternative solvent-free manufacturing process led to the Hot melt extrusion process using a twin-screw extruder. The TSE process initially developed using a Leistritz 18 mm intermeshing corotating twin-screw extruder was successfully scaled up to a Leistritz 50 mm extruder for the commercial production. The extrusion processing time is less than 1 minute for the batch size of 5000

CASE STUDY 3

Improving processability of API

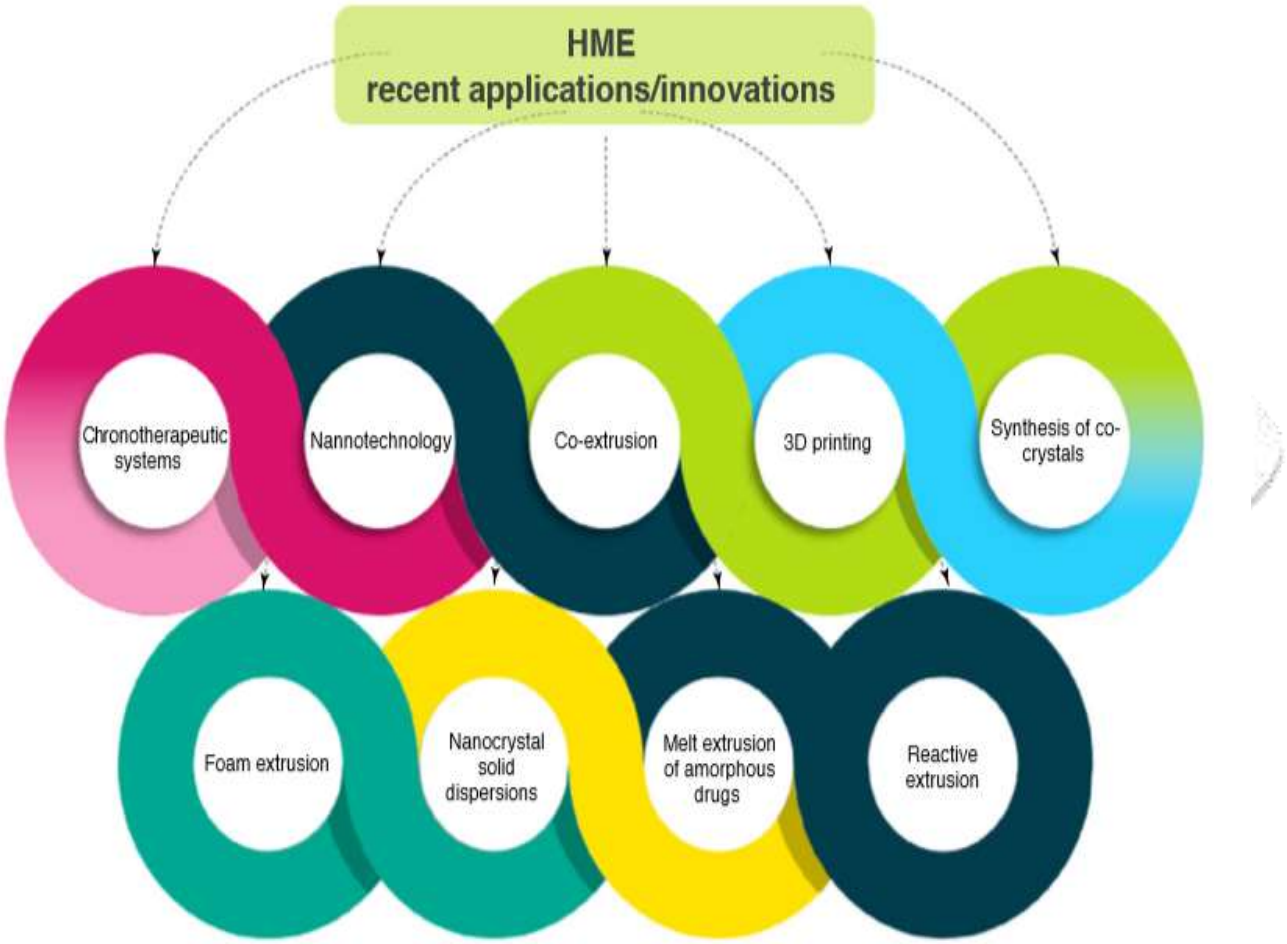
For example, metformin is widely used as an antidiabetic drug. But due to the high aqueous solubility, many formulations challenges are faced by the formulator.

1) As the dose is so high high drug loading is required.
2) Many formulation hurdles will be due to API property.
3) During wet granulation due to high water solubility, the crystal structure was formed in the hopper and affect the flow of the blend.
4) Large processing excipients were used.

Using melt granulation, can overcome all of the above problems, hydroxyl propyl cellulose is used as the binder which melts in the extruder and granules are formed. Tablet hardness of MG tablets was also found to be less sensitive to changes in moisture content during compression and subsequent storage. The low-moisture contents of the granules (about 0.2% w/w) is believed to be conducive to averting moisture-induced physical transformations in metformin HCl tablets, thus avoiding the change of tablet hardness with time, variable powder flow behavior, and problems with dissolution stability. In addition, the study also shows that the TSE granulation process can decrease the need for relatively large amounts of excipients often required for overcoming processing challenges posed by API physicochemical and mechanical properties, thus reducing tablet sizes of high-dose drugs.

Conclusion

The extrusion technique is coming up with novel approaches for the development of the new dosage forms. Hot melt extrusion, melt granulation and continuous wet granulation are studied widely to overcome many formulations problems like enhancing solubility, API processing improvement. ..New developments like nano-suspension using hot-melt extrusion, chrono-therapeutic systems, co-extrusion, co-crystal synthesis can be done. Twin-screw extruder process designing is a complex process, but once set gives reproducible output. The scale-up approach for the extruder is different from the traditional types of equipment As the application of extrusion is increasing, simulation of the process is becoming essential to have a proper understanding of process new software like Ludovic, helps to simulate the extruder design as well as can also suggest the materials to be used in HME.



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