Scientific Pharmaceutical Compounding using Hot Melt Extrusion

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Abstract

Pharmaceutical Compounding using Hot Melt Extrusion (HME) involves achieving a homogenous solid dispersion or solution by mixing and/or melting API with one or more excipients such as polymers, lipids, surfactants, diluents, lubricants, glidants, plasticizers and other modifiers for the purpose of stabilization, bio-availability enhancement, controlled release or taste-masking and improved delivery especially in oral and transdermal systems. Important requirements are to avoid drug degradation that could result in related substances or impurities and to achieve the required morphology or structure in the compounded mass. Applications in information technology grew sharply with the improvement in the process capability of the CPU. Likewise, applications in pharmaceutical technology are influenced by the process capability of the Extruder Processing Zone (EPZ) of the co-rotating twin-screw compounder. A ten-fold improvement in EPZ process capability accompanied by precise control of shear rates, kneading cycles and stirring rates can usher rapid growth of applications in pharmaceutical technology. This paper presents a 21st century outlook to high performance twin-screw hot melt extrusion which can also lead to more scientific compounding.

Introduction

By the middle of the 20th century, extrusion equipment based on a single screw were well established in rubber applications and various process industries. Specialized devices such as Banbury mixers were also available for intensive mixing of viscous materials. Two and three roll mills were also employed in preparing inks, paints, adhesives, ceramics and a variety of other materials. However, the need for a device that can continuously process with self-cleaning ability a chemical reaction that results in increase of molecular weight or viscosity without gelling spurred the development of newer extrusion technology that would later change plastics processing forever. The early co-rotating twin-screw extruder was conceived as a reactor vessel where control was needed in the positive movement of the molecules with the possibility of mixing or stirring action.

Roberto Colombo (1938) of LMP, Turing developed the first commercial co-rotating twin-screw and sold it to I.G. Farben. This design was licensed to manufacturers in France (now Clextral), England (R. H. Windsor) and Japan (Ikegai). Bayer-werk of I.G. Farben formed the High Viscosity group to develop further the extrusion technology for reactive extrusion. The development of co-kneader, counter-rotating twin-screw devices and the co-rotating twin-screw devices were pioneered by the team working under Dr. Walter Meskat. Booy (1978) provides the details of the work by Erdmenger (1944) who was assigned the task of engineering the co-rotating extrusion technology which was one of the three extrusion concepts that the high viscosity group led by Meskat pursued.

Erdmenger (1944) conceived the exact geometry that leads to perfect wiping of the screw profile in a co-rotating twin-screw extruder with one, two and three lobed designs. Padmanabhan (2000) showed ways to create perfectly wiping profile that does not have integer lobes bringing forth fractional lobed elements. During the last few decades, this technology has revolutionized plastics processing in the same way a personal computer transformed information processing. Many manufacturers making equipments with competing technologies have changed their products to co-rotating technology. While a counter-rotating extruder becomes a positive displacement "plug" flow device, a co-rotating extruder works similar to a single screw with some beneficial features. It offers an opportunity to work on the material by the application of forces that shear or smear the material, elongate, re-orient, compress or fold the material while retaining the control over the time the material is subjected to this rigor.

The Shear experienced in a roll mill is due to differential speeds of the drum. Shear gaps of 0.3mm to 2mm are used to maintain shear rates of 500 1/s to 3000 1/s. The material typically spends only a fraction of second in these high shear zones. The process generally does not involve taking advantage the elongational flow at the nip of the drums due to nature of viscosities involved. On the other hand, a roller compactor and a counter rotating twin screw extruder allow utilization of elongational flow stream at the nip area either under an up-stream feeding head or using a down-stream pressure head. The dispersive kneader family comprising of Banbury mixers and other continuous mixers have an altogether different action. This action is characterized by stretching or elongation the material followed by twisting or folding and finally squeezing the material either gently or suddenly. This action is also the commonly used action in the kitchen for kneading of materials in order to achieve wetting. The Co-kneader provides another action. It allows flow lines of the material to be disruption causing turbulence and stirring.

So far, stirring without pressure build up was only uniquely possible in a co-kneader allowing several applications involving materials with low sintering coefficient to be mixed efficiently.

Table 1. Mixing actions in various mixing equipments

Type of Mixing Equipment	Action
Roll mill with differing drum speeds	**Shear**
Roller compactor	**Elongational strain under a feeding head**
Counter-rotating extruder	**Elongational strain under a pressure head at die**
Dispersive Kneader or Banbury Mixer	**Wetting or Kneading action – Cycles of elongation, folding or twisting and squeezing.**
Co-kneader	**Stirring with some shear**
20th Century Co-rotating twin-screw	**All actions in a force cocktail called kneading**
21st Century High Performance compounding on OMEGA & OMICRON co-rotating twin-screw	**Separation of actions with greater control over shear, wetting and stirring**

The co-rotating twin-screw has always possessed the ability to induce all such actions on the material. The Kneading blocks in a co-rotating twin-screw extruder offers a versatile force cocktail of shearing, elongating, kneading and stirring actions. This led to a growth of applications in compounding. The ability to apply some of these actions in the pure form – kneading or stirring alone as would a dispersive kneader or a co-kneader does at different zones of the co-rotating twin-screw extruder is of great importance in the achieving process capability and economic viability in new generation of applications.

Process Window

The process window of the co-rotating twin-screw extruders was broadened when starve feeding was introduced. The introduction of starve feeding has meant that throughput is independent of screw speed. The process window consists of the range of residence time (controlled by throughput) and specific energy input (controlled by screw speed and screw design). However, the process window is not only constituted by the range of control over residence time and energy input but also the control over the location and extent of mixing actions.

A 60mm compounding equipment has approximately 4 liter capacity. During the 1950s, such equipment were available with a small motor power of 15kW or less. The material gradually moved through this equipment spending as much as 400 seconds to melt and homogenize. Recently, such equipment were fitted with a motor of 250 kW and 500 kW of power. It takes as little at 8 or 12 seconds for the material to be processed. A small vessel size and greater power capacity is capable of reducing the time for processing. To increase the extruder power, compounding equipment can be engineered with more torque or more speed. Table 2 provides the performance of the extruders over the years characterized by mean residence time.

Table 2. Improvements in Mean Residence Time

Year	Speed (RPM)	Power (kW)	Output (kg/h)	Mean Residence Time (s)
1956	150	12	25	410
1970	300	30	100	120
1983	600	120	500	25
1995	800	250	800	16
2004	1200	500	1500	8

Shear gaps of 3mm between screw flights are common in low performance equipment. In medium and high performance extruders, the shear gap in the intermeshing zone of the equipment is in the range of 0.5 to 1 mm (Fig. 1). In all extruders under fully filled condition, a pressure peak is created at the intermeshing zone resulting in flow through the screw to screw gap – the space between the screw surface labeled A and B in figure 2. In high speed extruders, the pressure peak can be created even in a partially filled zone.

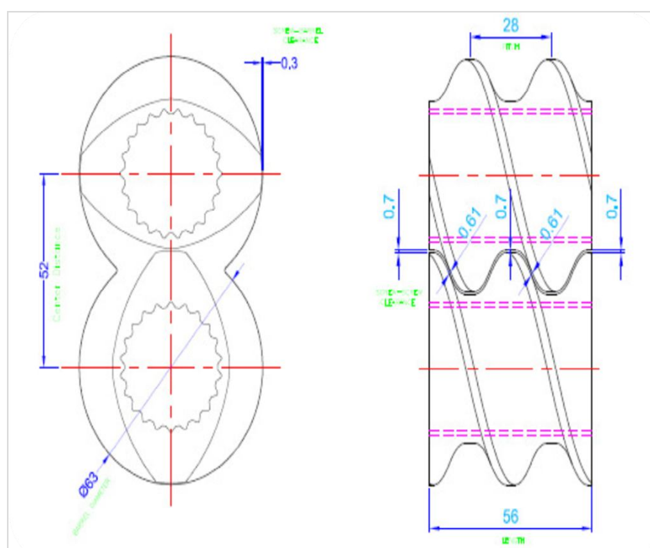

Figure 1. Typical clearances in the screw elements

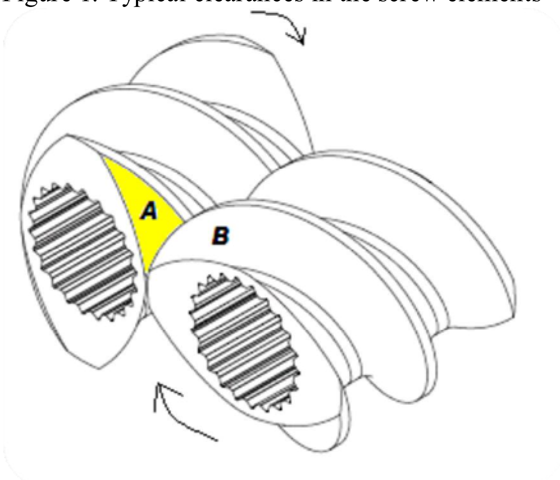

Figure 2. Interacting surfaces at the intermeshing zone

Mean shear rate (at the screw flight) $= \pi D n / h$
Where D is the Barrel Diameter
n is the revolutions per second (N / 60)
and h is the flight depth

Peak shear rate (at the intermeshing zone) = $2 \pi a n / c$

Where a is the center distance
c is the screw to screw shear gap, usually 0.5 to 3 mm

Table 3 Shear in co-rotating twin-screw extruders

Speed RPM	Mean Shear rate (1/s)	Peak Shear rate (1/s)	Mean Residence Time (s)	Total Shear
150	150	750	410	61500
300	170	1500	120	20400
600	300	3000	25	7500
800	400	4000	16	6400
1200	600	6000	8	4800

During the last 50 years, the total shear input has considerably decreased leading to better energy efficiency. On the other hand, the high peak shear leads to increased chances of degradation. Moreover, the non uniformity of shear leads to difficulties in achieving the required dispersion in a consistent manner. Therefore, despite progress in mechanical ability of the extruder, the process capability of a high speed, high torque equipment has been sub optimal. As a result, according to survey quoted by Potente (2006), only 10 to 20% of the processors maintain screw speeds greater than 600 RPM due to the fear of reduction in product quality. In other words, a residence time of 40 seconds and above is considered standard. A quantum jump (10x) in process capability that allows process to be achieved in four seconds of residence time is possible with high performance compounding with the following features.

21st Century Perspective

The co-rotating twin-screw extruder is a horizontal mixer, in fact a continuously stirred vessel, in which the speed of extruder screw controls the energy transfer capability of the vessel.

To fully optimize the working of the mixer, we need to be able to

i. Have control over residence time
ii. Have better self cleaning and as a result shear uniformity
iii. Have full range of pure mixing actions viz. kneading and stirring.
iv. Have scalability across platforms.

Control over Residence Time

The residence time of the material depends on the feed rate of the material that flows and fills a certain portion of the available free volume inside the co-rotating twin-screw extruder from the time of entry until exit through a die. Achievable feed rate is limited by screw speed. Since power is also limited by screw speed, the joint limitation was never considered a significant problem as long as materials are not feed limited. The requirements to process low bulk density polymer resins in the form of powder together with various low bulk density fillers is on the rise and affecting many applications. Feed limitation can be overcome by using shovel elements (Fig. 3).

Figure 3. Shovel Elements for overcoming feed limitation

Introducing powders in a co-rotating extruder has been a challenge for years. Over sizing the extruder to meet desired output, not only compromises the energy efficiency but also lowers the process capability of the extruder. Hence, for a given formula composition, adaptation of the equipment/screw configuration to address the flow properties or throughput rate is highly advantageous. Normal screws work similar to a conventional snow plough. The face is slanted forward to throw the material to the side. In an extruder, this reduces intake capacity due to fluidization. If a snow plough is fitted with a shovel face, it will quickly build a mound of snow in front of it. Such an event in an extruder will be termed as making the process torque limited from being feed limited. Importantly, the intake capacity increases almost linearly as the screw speed is increased allowing the extruder to be used optimally. Normal screw elements do not exhibit this ability because after attaining certain screw speed, intake capacity remains low due to fluidization of the material.

Better side-feed design with deeper flighted side-feeders and side ports with vacuum stuffer are also responsible for overcoming feed limitation without being limited by screw speeds for increasing intake capacity.

Better Self Cleaning and Shear Uniformity

It is well-known that cleaning can occur without contact depending on the gap, material viscosity and pressure heads. Polymeric materials under process conditions typically have viscosities in the region of 100 Pa.S to 1000 Pa.S. Under these viscosities, a pressure of 5 MPa is enough to squeeze material through a gap of 0.5mm. When a screw to screw gap of less than 0.2mm is maintained in the intermeshing zone, the required pressure will be 15 times greater. This would generally exceed the pressure building capability of the extruder. Since no material passes through the gap, the material does not experience shear or screw wear. In other words, self cleaning effectively leads to shear uniformity.

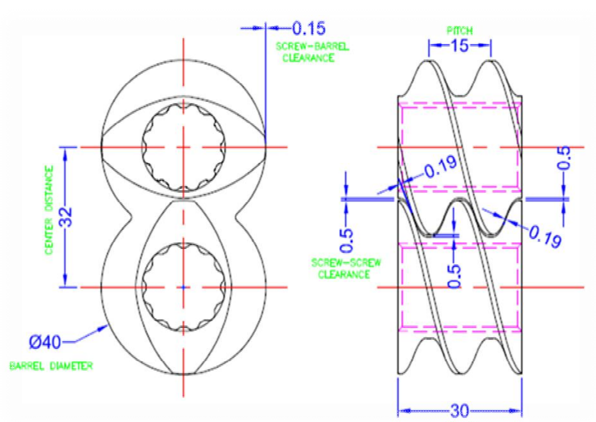

Figure 3. Shear gap in OMEGA extruder

Gearboxes that have lower axial play and reduced back lash and equal angular deflection are required to be used in such precision engineered screw shaft assemblies.

Pure Mixing Actions

Kneading Action

Fractional Kneading Blocks (FKB) (Fig. 4) have an enhanced melting and mixing efficiency when compared to normal kneading blocks as a result of its ability to stretch, fold and squeeze material in closely operated kneading cycles. It is possible to design the fractional lobes to eliminate shear peaks and transfer energy more uniformly to the materials being processed. This increase in the uniformity and intensity of energy input results in the requirement of a much shorter kneading section, up to 50% shorter than a typical kneading section using standard kneading blocks. This reduces energy consumption by the extruder and ultimately enables an increase in throughput and line capacity. Improvements can also be realized in product quality and overall production efficiency. FKB's are particularly effective in mixing different materials with a wide discrepancy in melt viscosities, such as compounding high temperature engineering thermoplastics with low viscosity resins and liquid additives.

Figure 4. Fractional Kneading Blocks (FKB)

The FME elements (Fig. 5) are a unique family of mixing elements that offer the ability to avoid the effects of pressure peaks and shear peaks while imparting a high degree of elongational mixing in a constrained space. Materials passing through FME's experience a very uniform and effective energy input.

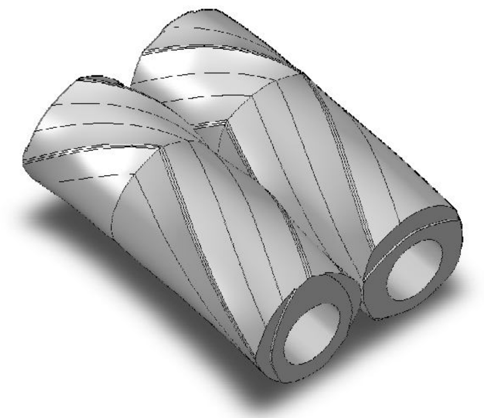

Figure 5. Fractional Lobed Mixing Elements (FME)

Stirring Action

DSEs (Fig. 6) are novel mixing elements that feature corresponding pins and grooves to impart highly effective dynamic stirring action in an unconstrained, open environment. The open architecture of the element, which couples mixing with forward conveying, prevents shear and heat generation that can occur when a highly filled resin comes into contact with typical mixing elements. The self-wiping design of the element prevents stagnation and degradation that can occur with many distributive mixing elements. DSEs reproduce the gentle mixing action of co-kneaders in a twin screw extruder, such that existing twin screw extruders can now process materials once bound to co-kneaders. DSEs work very well for the pre-wetting and pre-mixing of high levels of APIs and fillers prior to exposing them to a confined kneading environment, thus eliminating the intense particle-to-particle shear that can occur when un-wetted fillers are compressed.

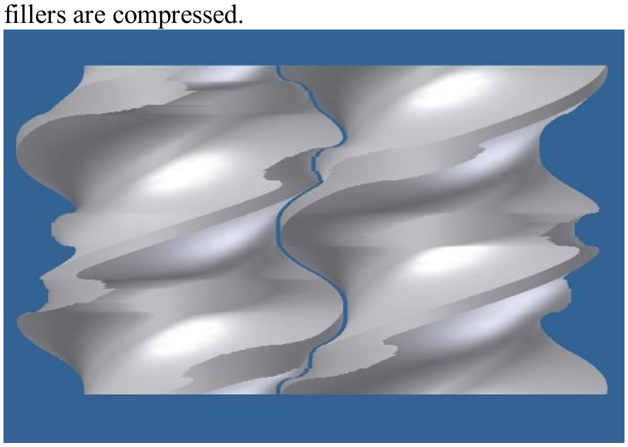

Figure 6. DSEs with mixing grooves and pins

Process Scalability

Use of the same Do/Di leads to identical mean shear rates at the same extrusion speed. However, shear rates can be maintained across different Do/Di platforms by adjusting the screw speed by the shear factor. Extruders that are built with-out shear uniformity would have the additional problems of peak-shear effects that are diameter dependent. Therefore, scalability problem arises due to peak shear effects. Further, variations in process conditions during scale-up arises primarily due to the mismatch between mixing rates (a function of area) and residence time changes (a function of volume). Therefore, to maintain the same residence time, the output has to be changed in the ratio of the cube of diameters. Design of mixing elements and Kneading blocks should be able to provide adequate mixing rate. It is possible to design these elements to have the same mixing area.

Conclusion

The co-rotating twin-screw extruder is a versatile device for material preparation and modification. The earliest generation extruder built in the 1950s had mean residence time of several minutes. During the last 50 years, the residence time has been reduced to half its original value every ten years or so with steady increase in shear capacity. By the end of the 20th century, extruders had the capability to reduce the time to less than 10 seconds. The inability to control peak shear rates (that could exceed 5000 sec^{-1}) and a lack of a good understanding of the forces experienced by the material inside the extruder resulted in the inability to utilize the abilities of the system. This paper outlined some of the process characteristics that allow for utilization of the technology with a tenfold improvement in process capability enlarging the anticipated potential for HME in new pharmaceutical applications development.

References

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