Implantable drug delivery

Innovations in hollow tube implants for targeted drug delivery systems

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Introduction

Hot-melt extrusion (HME) has rapidly gained importance in the pharmaceutical industry due to its unique advantages over traditional manufacturing methods.[1] These advantages include a solvent-free and dust-free process, fewer processing steps, reproducibility with minimal batch-to-batch variation, and the ability to facilitate continuous manufacturing. HME provides an efficient way to incorporate APIs into polymer-based rods or tubes that can be cut and shaped to form customized implants for drug delivery.

One such novel drug delivery system, subcutaneous implants, has emerged in recent years. These implants are usually in the form of cylindrical rods made from a polymer matrix that incorporates the active pharmaceutical ingredient (API) for sustained release. These implants enable site-specific, controlled release of the API, allowing for treatment durations of weeks to years. Moreover, they offer higher patient compliance compared to oral drug delivery systems. The applications of subcutaneous injectable implants span a broad range, from contraception to chronic disease treatments. HME is proving to be an excellent technique for producing a variety of these specialized drug delivery implants.

Types of implant designs

Matrix type implant design

In matrix type design, the drug is dispersed uniformly within a polymer matrix. This type of implant is characterized by a high initial release rate, often referred to as a “burst” release, followed by a more gradual release. The release rate is influenced by the API loading, morphology, and particle size of the API. This matrix type is typically used for applications requiring a rapid onset of action followed by sustained release.

Reservoir type implant design

In a reservoir type design, the drug is dispersed in a core that is surrounded by a pure polymer membrane. The core can be a solid dispersion or a solid solution of the API in the polymer. Alternatively, the API can be dispersed in a lipid liquid filled into hollow tubes that serve as the release membrane. This type of implant provides a more controlled and consistent release profile. Reservoir type implants are suitable for applications requiring precise control over the drug release rate.

Use of hollow tubes in reservoir type designs

Hollow tubes have gained significant attention in the field of controlled drug delivery due to their unique ability to encapsulate and release therapeutic agents in a targeted and sustained manner.[2] The manufacturing process of hollow tube-based implants consists of three main steps:

1. Extrusion of capillary (hollow tube)
2. Filling of capillary with liquid
3. Sealing of open ends

These steps ensure the production of high-quality hollow tubes suitable for their intended use. This application note provides a comprehensive overview of the process and benefits of using hot-melt extrusion for the manufacturing of hollow tube implants, highlighting the critical steps and conditions necessary for successful implementation.

Materials and methods

Materials

The findings here are derived from multiple trials conducted using commonly used biodegradable polymers such as polylactic-co-glycolic acid (PLGA). The powder blend PLGA RG502H was kindly provided by Evonik Industries AG (Darmstadt, Germany).

Methods

The HME process comprises several steps, including material feeding, plastification and compounding, extrusion and shaping, precise diameter measurement, diameter control loop to conveying mechanism, and precise cutting. The setup included the Thermo Scientific™ Pharma™ 11 Twin-Screw Extruder, the gravimetric RotoTube feeder, and the Thermo Scientific™ CaliCut™ Post-Extrusion System to perform all the process steps (Figure 1).

Figure 1. Extrusion setup for hollow tube extrusion with Pharma 11 twin-screw extruder, gravimetric RotoTube feeder, Pharma 11 catheter die, and pulling and cutting to the required length and diameter control via the CaliCut post-extrusion system.

The material, a blend of powders, was continuously fed with a gravimetric feeder control into the co-rotating Pharma 11 twin-screw extruder with a functional length of 40 L/D. This feeding system could control feed rates of around 100 g/h. The Pharma 11 twin-screw extruder was equipped with a standard HME screw design with two kneading blocks (30°, 60°, and 90°). Additionally, an innovative Pharma 11 catheter die (Figure 2) with less dead volume was mounted to extrude the material as a hollow strand. The catheter die allows the production of different outer (OD) and inner diameters (ID) depending on the selected inserts. In this study the material was extruded through a catheter die with defined inner and outer diameters of ID = 1.55 mm and OD = 2.3 mm to shape the hollow implant accurately to the targeted implant size.

Figure 2. Pharma 11 catheter die.

The extrusion temperature was gradually increased from 25°C to 100°C across the 8 different zones and the catheter die. The screw speed was kept constant at 100 rpm.

The CaliCut post-extrusion system is an advanced instrument designed for precise calibration of polymer strands and cutting them into well-defined pharmaceutical implants, ensuring compliance with GMP and 21 CFR part 11 regulations. The extrudate can be taken directly through a 1-axis laser diameter measurement and onto the conveyor belt without a major cool down. Based on the laser measurement, the belt speed can be adjusted to pull the strand, enabling the diameter to be adjusted within set tolerances to maintain the outer diameter.

Before a strand enters the cutting section of the instrument, the belt length ensures sufficient cool down of the strand, so cutting can be executed with maximum precision. The cutting of an implant is a crucial step, and smooth cutting surfaces depend greatly on polymer formulation and the cutting method applied. For this setup the rotary cutter was utilized. The rotating knife was fitted to cut the hollow strand into 10 mm hollow tubes which were then collected.

Results and discussion

The blended powder mixtures were successfully extruded within an optimal temperature range, ensuring stable process parameters such as extrusion and die temperature, screw speed, and feed rate. Accurate feeding of the powder blend was crucial to maintain tight dimensional tolerances of the implants. The preprocessing of the powder blend using hot-melt extrusion for pellet production improved flowability and ensured more accurate material feeding in the second extrusion.

During the extrusion process, the polymer was melted and compounded homogeneously using a twin-screw extruder. Key process parameters included barrel and die temperature; screw design and speed; and throughput. The maximum throughput was limited by the resulting pressure of the extruded material.

It was essential to keep the screw speed and temperature as high as necessary for processing but as low as possible to avoid degradation and generation of impurities. Good extrudability was linked to hollow tubes exhibiting the following characteristics:

1. Maintained shape—The hollow tubes maintained their shape without collapsing or expanding upon exiting the die
2. Uniform diameter—Inner diameter (ID) and outer diameter (OD) stayed consistent
3. Smooth surface—No pores formed, ensuring a consistent release profile

The die temperature significantly influenced the final shape stability of the hollow tube due to the viscosity properties of the extruded melt. Higher process temperatures at the die tended to cause the hollow strand shape to collapse. The diameter was measured by a 1-axis laser measurement, and the conveying speed was adjusted based on the outer diameter value, resulting in any corrections of the strand diameter. The inner diameter and wall thickness were adjusted via controlled airflow through the inner die pin insert, resulting in specimens with consistent wall thickness, as seen in the microscope image (Figure 3).

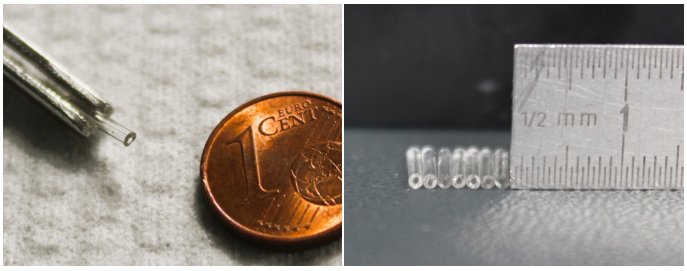

Figure 3. Extruded hollow tubes with an outer diameter of 1.5 mm, wall thickness of 0.4 mm, and length of 10 mm.

The hollow strand temperature was controlled for constant conveying and accurate cutting in the CaliCut conveying chamber. The final hollow tube implants could be easily filled with a liquid via capillary forces (Figure 4) and are ready for the next possible processing step, the sealing of the openings.

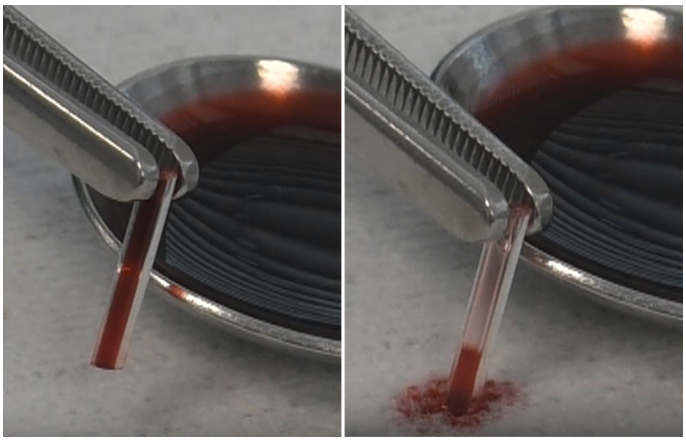

Figure 4. Hollow tube filled with colorant liquid demonstrating easy filling and emptying due to capillary forces.

Conclusion

Injectable hollow tube implants offer a promising parenteral drug delivery system for the safe administration of highly potent drugs. The HME process provides reliable technology for continuous manufacturing of these implants with minimal tolerances and excellent content uniformity. The ability to fill these hollow tubes with lipid-based APIs via capillary forces underscores their potential in providing targeted and sustained drug delivery. This innovative approach enhances patient compliance and broadens the scope of applications, from contraception to chronic disease treatments. Future research should focus on further optimizing the HME process and exploring a wider range of polymers and APIs to expand the versatility and efficacy of hollow tube drug delivery systems.

References

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