Hot Melt Extrusion

Innovations in Hollow Tube Implants for Targeted Drug Delivery Systems

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Introduction

Over the past decade hot melt extrusion (HME) has rapidly gained importance in the pharmaceutical industry due to its unique advantages over traditional manufacturing methods [1]. These include a solvent-free and dust-free process, fewer processing steps, reproducibility with almost no batch-to-batch variation, and the ability to facilitate continuous manufacturing. To ensure excellent content uniformity and geometrical tolerances, the technology of hollow tube implant manufacturing using HME is discussed in this study, with a focus on the most critical process steps.

Subcutaneous implants have emerged as a novel drug delivery system, usually in the form of cylindrical rods made from a polymer matrix that incorporates the active pharmaceutical ingredient (API) for sustained release. Subcutaneous 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 various chronic disease treatments. These implants are manufactured using hot melt extrusion or co-extrusion techniques. There are several types of implant designs:

Matrix type implant design

The drug is dispersed in a polymer matrix.

- Release rate:
  - Typically higher initial release (“burst”)
  - Higher influence by API loading
  - Higher influence by morphology and particle size of API

Reservoir type implant design

The drug is dispersed in the core while it is surrounded by a pure polymer membrane. The core can have different configurations:

- Solid dispersion (matrix + membrane)

- Release rate:
  - Controlled by membrane characteristics
  - More consistent release profile

- Solid solution of API in polymer core in which the API dispersed in a lipid liquid filled into so-called hollow tubes that serve as a release membrane (liquid core + membrane)

- Release rate:
  - Controlled by membrane characteristics
  - Zero order release

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 tubes 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.

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.

Materials and methods

Materials

This study's findings are derived from multiple trials conducted using commonly used biodegradable polymers such as polylactic-co-glycolic acid (PLGA). The powder blend PLGA RG502H were 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 is including 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).

The material is continuously fed with a gravimetric feeder control into the co-rotating Pharma 11 mm twin-screw extruder with a functional length of 40 L/D. This feeding system could control feed rates of around 100g/h. The Pharma 11 twin-screw extruder is equipped with a standard HME screw design with two kneading blocks (30°, 60°, and 90°). Additionally, an innovative Pharma design catheter die with less dead volume is mounted to extrude the material as a hollow strand. The catheter die allows different outer (OD) and inner diameters (ID) depending on the selected inserts. In this study the material is extruded through a catheter die with defined diameter ID = 1.55 mm and OD = 2.3 mm to shape the hollow implant accurately to the targeted implant size.
The extrusion temperature is gradually increased from 25 °C to 100 °C across the 8 different zones and the catheter die. The screw speed is 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 is adjusted and pulls 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 is equipped. The rotating knife is fitted to cut the hollow strand into 10 mm hollow tubes which are then collected.

The produced hollow tube implants are evaluated via a Leica DM2700 M RL microscope (Figure 2).

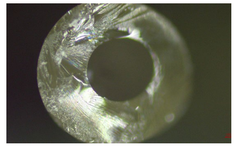


Figure 2. Microscopy image of hollow tube edge

Results

Feasibility of hollow tube extrusion

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 (HME) for pellet production improved flowability and ensured more accurate material feeding in the second extrusion.

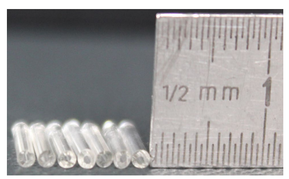
During the extrusion process, the polymer was melted and compounded homogeneously using a twin-screw extruder. Key process parameters included barrel and die temperature, screw design and speed, and throughput. The maximum throughput was limited by the resulting pressure of the extruded material.

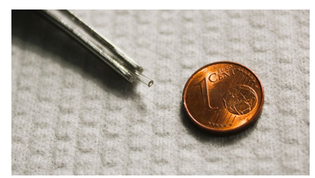
It was essential to keep the screw speed and temperature as high as necessary for processing but as low as possible to avoid degradation and generation of impurities. Good extrudability was linked to hollow tubes exhibiting the following characteristics:

1. Maintained shape without collapsing or expanding upon exiting the die
2. Uniform inner diameter (ID) and outer diameter (OD)
3. Smooth surface without pores

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 a correction 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 is 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 is ready for the next possible processing step, the sealing of the openings.

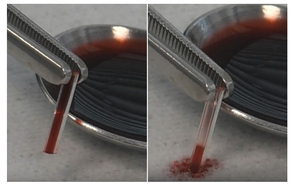


Figure 4. Hollow tube filled with colorant liquid demonstrating easy filling and emptying due to capillary forces.

Conclusions

Injectable implants offer a promising parenteral drug delivery system for the safe administration of highly potent drugs. Hot melt extrusion is a reliable technology for continuous manufacturing of hollow tube implants with minimal tolerances and excellent content uniformity, which is crucial for the reliable sustained release of active pharmaceutical ingredients (APIs). The stable manufacturing process relies on consistent feeding of the materials. Compounding of the ingredients and strand shaping are achieved in a single processing step utilizing the twin-screw extruder. The successful implementation of these hollow tube implants, with their ability to be filled with lipid-based APIs via capillary forces, underscores their potential in providing targeted and sustained drug delivery. This innovative approach not only enhances patient compliance but also 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

[1] Almeida, A.; Clayes, B.; Remon, J.P.; Vervaet, C. in Hot-melt extrusion, ed. D. Douroumis, Wiley, 2012, 43-69.
[2] Bebernik P., Frenzel J.L., Beck L., Duaer K., Wagner K.G.; Rational design and DoE based prediction model for levodopa gastroretentive systems based on hot-melt tube extrusion; Journal of Drug Delivery Science and Technology, Vol. 111, 107201.

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