Optimizing the HME process for precise manufacturing of subcutaneous drug delivery implants: key considerations for quality and efficiency

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Purpose

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.

Objectives

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 automated implant manufacturing using HME is discussed in this study, with a focus on the most critical process steps.

Methods

This study's findings are derived from multiple trials conducted using commonly used biodegradable polymers such as polylactic-co-glycolic acid (PLGA), in which the API is uniformly incorporated into the melted polymer during the HME process. The HME process comprises several steps, including powder feeding (1)), plastification and compounding (2)), extrusion and shaping (3)), precise diameter measurement (4)), diameter control loop to conveying mechanism (5)), precise cutting, and quality sorting (6)). The Thermo Scientific™ Pharma *mini* Implant Line includes all the aforementipned process steps (see Figure).

Pharma *mini* Implant Line for production of injectible implants.

The Pharma *mini* HME Conical Twin-Screw Extruder is utilized in co-rotation mode. The implants produced are evaluated via SEM imaging with the Phenom XL G2 Desktop SEM. This study provides a summary of the most crucial process points for each step of the manufacturing process.

Rheology is a powerful tool to get an insight about the flow properties of polymer melts. Besides this, rheometers equipped with solid sample clamps can be used to determine the glass transition of polymers Utilizing dynamic mechanical thermal analysis (DMTA). DMTA is known to be much more sensitive towards detecting glass transition temperatures compared to other techniques like differential scanning calorimetry (DSC) [2]. Hence, a HAAKE™ MARS ™ iQ Air Rheometer is used to quantify the thermo-mechanical properties of the polymers used in this study.

Results

1.) Powder feeding

The powder blend of the API and the excipients is continuously fed into the extruder. Accurate powder feeding is essential to obtain implants with small tolerances in dimensions.

The material properties of the powder blend are the most crucial factors in this process unit. The blend needs to be homogenous and stable, obtaining a good flow behavior (especially, considering powder bridging and electrostatic charging). To improve flowability of the material a preprocessing using a continuous melt granulation is recommended. Different feeders are available to reach a constant material flow. A gravimetric twin-screw feeder gives the best output starting from a feed rate of 20 g/h.

2.) Plastification and compounding

The polymer is molten, and all ingredients are compounded homogeneously by the twin-screw extruder. Process parameters such as the barrel and die temperature, screw speed and throughput into the extruder are crucial.

The maximum throughput is limited by the line speed of the extruded material. Typical throughputs into the Pharma mini HME range between 2 and 100 g/h, screw speeds between 10 and 360 1/min and temperatures up to 280 °C.

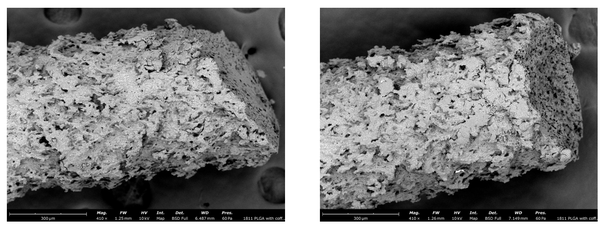
Always keeping the screw speed and the temperature as high as needed to process the material, but as low as possible to avoid degradation.

3.) Extrusion and shaping

The material is extruded through a die with defined diameter to shape the implant accurately. The die size, and temperature have a big impact on the product quality. As can be seen on the SEM pictures of ophthalmic PLGA-based implants, the die temperature influences the final shape of the cut. This is due to the cooldown of the extrudate. Very cool extrudates tend to break rather than being cut properly.

4.) Precise diameter measurement and control loop to conveying mechanism

The diameter is measured by a 2-axis laser gauge to check diameter and ovality. Based on that value the speed of the pulling wheel is adjusted resulting in a correction of the strand diameter. The temperature of the strand needs to be controlled in order to allow a constant conveying and accurate cutting.



SEM images of the implant edge after continuous cutting extruded at 135°C (left) and 145 °C (right).

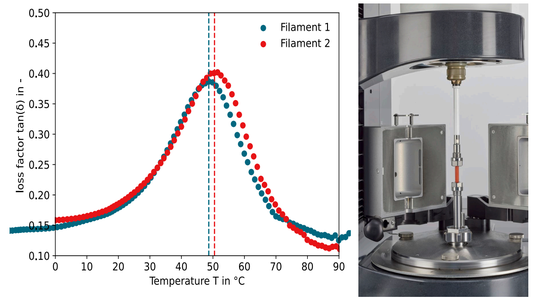
5.) Rheology/ Dynamic Mechanical Thermal Analysis (DMTA)

DMTA measurements were done in a temperature range from 0 °C to 100 °C with a heating rate of 2 K/min to obtain the thermo-mechanical properties of two extrudates with different API content.

In contrast do DSC, glass transition temperatures (Tg) obtained by means of DMTA are not acquired from the variation of the specific heat capacity but from changes in the temperature-dependent mechanical properties of a sample.

When performing DMTA measurements, Tg`s are typically derived from the maximum of the loss factor tan (d). Further evaluation methods, focusing on storage modulus G' or loss modulus G'' are also available.

In this case, the different API content leads the glass transition temperature to rise from 48.7 C for Filament 1 up to 50.5 °C for Filament 2.



DMTA thermogram of two different filaments with different API content (left) as well as the used rheometer configuration (right)

Conclusions

Injectable implants are a promising parenteral drug delivery system for a safe administration of high potent drugs.

Hot melt extrusion is a reliable technology to manufacture implants continuously within small tolerances and with good content uniformity. Consistent feeding is key in maintaining a stable implant manufacturing process.

Compounding of the ingredients as well as shaping of the strand is done within one processing step on the twin-screw extruder.

All unit operations from powder feeding to sorting are integrated in the Pharma Mini Implant Line.

Besides this, a rheometer can be used to obtain thermo-mechanical properties like the glass transition temperature of implants derived straight from the extrusion line.

References

1] Almeida, A.; Clayes, B.; Remon, J.P.; Vervaet, C. in Hot-melt extrusion, ed. D. Douroumis, Wiley, 2012, 43-69

[2] Jones, D.S.; Tian, Y.; Abu-Diak, O.; Andrews G.P; "Pharmaceutical applications of dynamic mechanical thermal analysis", Adv. Drug Deliv. Rev., 64, 2012, 440-448

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