Development of PLGA-Based Implants Using Hot Melt Extrusion for Sustained Release of Drugs The Impacts of PLGA's Material Characteristics

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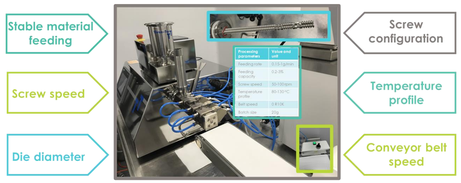
Purpose: Poly (lactic-co-glycolic acid), or PLGA, is one of the most extensively used copolymers for controlled drug delivery applications. There are many drug products (dosage forms) containing PLGA that are approved by the FDA and EMA for human use. Hot melt extrusion (HME) processed implant is one of the commercialized PLGA-based drug delivery products, which has solid, well-designed shape and rigid structures. These implants afford efficient locoregional drug delivery on the spot of interest for months or even years. In general, there are a variety of material, processing, and physiological factors that impact the degradation rates of PLGA-based implants and concurrent drug release kinetics. The objective of this study is to investigate the impacts of PLGA's material characteristics on PLGA degradation and subsequent drug release behavior from the implants.

Methods: Two grades of Viatel™ PLGA, with different co-polymer ratios, molecular weights, end groups, and levels of residual monomer, were formulated with two model drugs with different solubilities. A Three-Tec ZE 9 mm extruder (Three-Tec GmbH, Switzerland) equipped with a volumetric feeder was utilized to prepare PLGA/drug implants. The pre-cut implants were kept in a 50ml centrifuge tube fulfilled with 40 mL of dissolution media. The centrifuge tubes were incubated in a water shake bath at 37 °C for an extended time with multiple pre-defined sampling time intervals. The drug release profile was quantified by employing a high-performance liquid chromatography (HPLC). Morphology and property characterizations were studied and correlated with the dissolution performance.

Processing Setup and Formulations:



	Carbamazepine	Metformin Hydrochloride
Solubility in water at 25 °C (mg/L)	18	100,000
Melting point (°C)	189-190	218-220
Drug load (%)	60	15
Target implant diameter(mm)	1	1
Polymer carrier	PLGA 5003A Ultra and Regular	PLGA 7509E Ultra and Regular

Figure 1. Processing challenges for producing PLGA based implants via hot melt extrusion (HME) and model formulations contain two drugs with different solubility.

Carbamazepine Results:

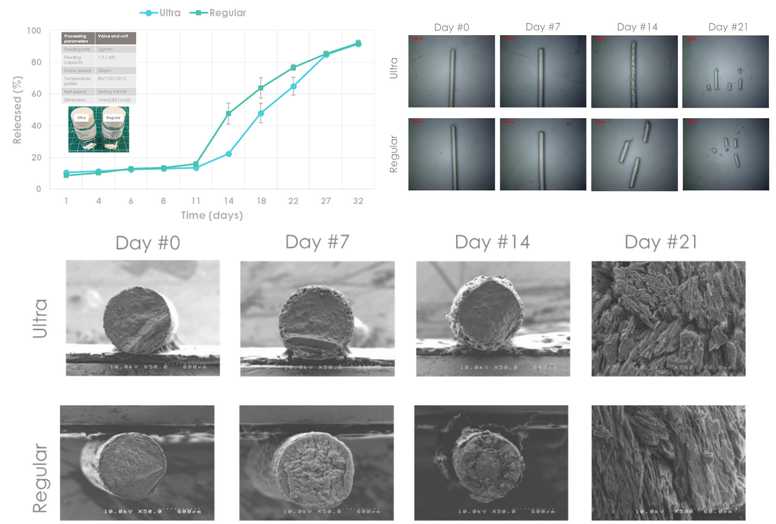
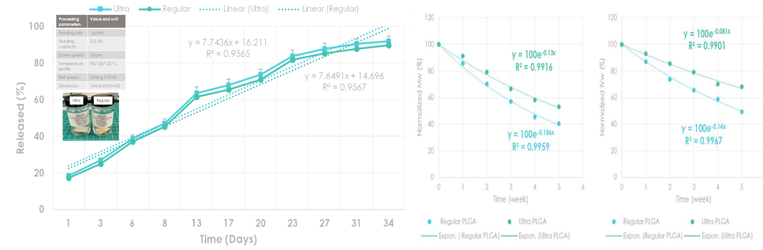


Figure 2. Although the regular PLGA implant displayed a similar release profile as the ultrapure up to 8 days, the onset and progress of its major release was shorter and faster. Additionally, SEM images confirmed that the regular implant degraded faster via a bulk erosion mechanism, conversely, ultrapure implant was surface erosion dominated.

Metformin Hydrochloride Results:



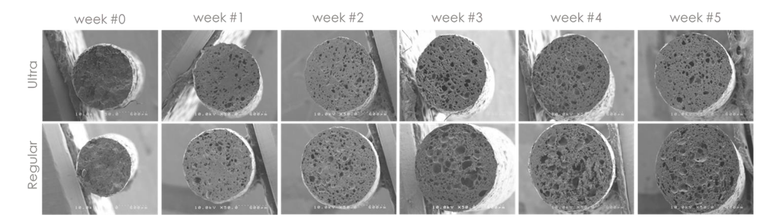


Figure 3. Implants of both grades displayed a zero-order metformin release profile. Neglectable differences were observed between the two grades, indicating that the release of the metformin was independent of the structure of the implant due to the high solubility of metformin. Substantial characterizations on the implant's morphology demonstrated that regular implant degraded faster, evidenced by more porous structure and faster reduction in both molecular weight and intrinsic viscosity than the ultrapure implant.

Conclusion: Polymer characteristics and quality are critical that impact the stability of the PLGA implant and subsequent release profile of the drug. New Viatel™ ultrapure bioresorbable polymers with supreme quality and purity open the door for optimal and innovative implant-based drug delivery systems.

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