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# The Impacts of PLGA's Material Characteristics on the Performance of PLGA-Based Implant Prepared by Hot Melt Extrusion (HME)

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## PURPOSE

Poly (lactic-co-glycolic acid), or PLGA, is one of the most extensively used polymers for controlled-release 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 implants are one of the commercialized PLGA-based drug delivery products, which has solid, well-designed shape and rigid structures. These implants allow efficient locoregional drug delivery for weeks to months. In general, there are a variety of material, processing, and physiological factors that impact the performance of PLGA-based implants. The objective of this study is to investigate the impacts of polymer material characteristics on PLGA-based implants degradation and subsequent drug release behavior from the implants.

## METHODS

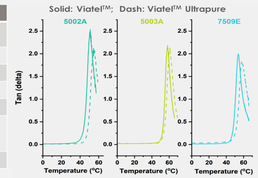
Three grades of Viatel™ PLGA, with different co-polymer ratios, molecular weights, end groups, and levels of residual monomer (Low: Ultrapure; High: Viatel), were formulated with three model drugs with different chemistries. A Three-Tec ZE 9 mm extruder (Three-Tec GmbH, Switzerland) equipped with a volumetric feeder was utilized to prepare PLGA/drug implants. Freshly manufactured extrudates were cut into implants with defined lengths containing a specified amount of drug. To assess the implant's erosion and degradation behavior and to evaluate their impact on the subsequent drug release performance, 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 shaker 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) system coupled with a photodiode array detector. In conjunction with the existing dissolution profile, the changes in the physiochemical characteristics of the implants through the dissolution period were monitored by light and scanning electron microscopes (SEM), and size-exclusion chromatography (SEC) measurement. Moreover, numerical evaluation and fitting were conducted to depict the PLGA degradation and subsequent drug release kinetics. Analytical quantification results were summarized and correlated with the experimental observations.

## RESULTS

### 1. Polymer characterizations

| PLGA | 5002A | | 5003A | | 7509E | |
|---|---|---|---|---|---|---|
| | Viatel™ | Viatel™ Ultrapure | Viatel™ | Viatel™ Ultrapure | Viatel™ | Viatel™ Ultrapure |
| Mn (Da) | $9.00\times10^3$ | $9.36\times10^3$ | $1.13\times10^4$ | $1.12\times10^4$ | $4.72\times10^4$ | $4.30\times10^4$ |
| Mw (Da) | $1.64\times10^4$ | $1.65\times10^4$ | $2.26\times10^4$ | $2.18\times10^4$ | $1.08\times10^5$ | $1.04\times10^5$ |
| Mz (Da) | $2.43\times10^4$ | $2.42\times10^4$ | $3.48\times10^4$ | $3.34\times10^4$ | $1.79\times10^5$ | $1.69\times10^5$ |
| Mw/Mn | 1.82 | 1.76 | 1.99 | 1.95 | 2.28 | 2.41 |
| Residual monomer (wt%) | 1.06 | 0.02 | 1.24 | 0.01 | 1.79 | 0.08 |
| $T_g$ (°C)* | 50.8 | 54.5 | 58 | 60.6 | 53.8 | 58.3 |

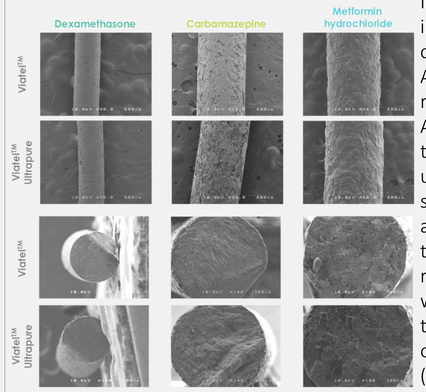
Note: * Measured by dynamic mechanical analysis (DMA).




Physicochemical characterizations exhibited that the purification process could largely maintain the targeted molecular weight and distribution and effectively remove the residual monomer and reduce its content in Viatel™ ultrapure grade to a relatively low level, precisely, less than 0.1wt%.

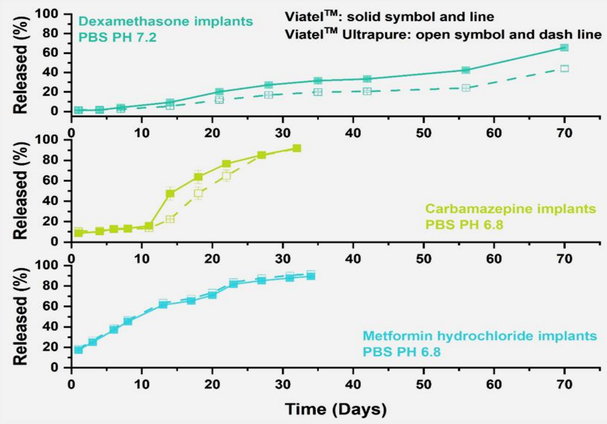
The plasticity of PLGA was inversely proportional to its molecular weight, however the residual monomer could impose a plasticizing effect to PLGA, which substantially increased its thermal plasticity and enhanced its thermal processability.

### 2. Implant characterizations



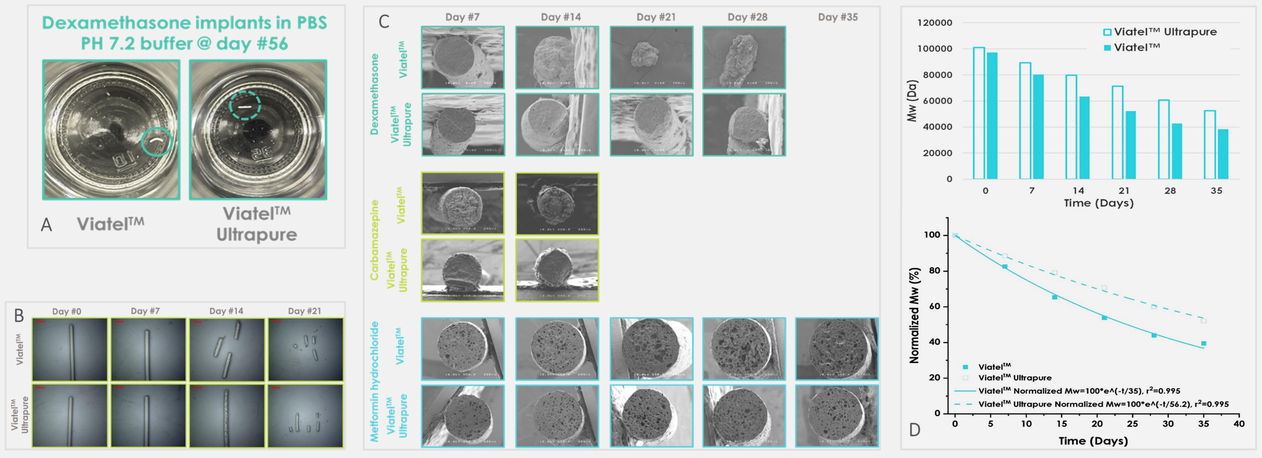

Implants' surficial and internal structures were characterized by SEM. All implants exhibited a rough, irregular surface. At the same processing temperature, Viatel™ ultrapure PLGAs led to a slightly worse surficial and interior structure than Viatel™ PLGAs did regardless the molecular weight difference, due to their lower contents of residual monomer (low plasticity).

### 3. Dissolutions




The implants with Viatel™ PLGA exhibited less burst release than implants with Viatel™ ultrapure PLGA, however, their onset and progress of the major release phase were shorter and faster than the Viatel™ ultrapure based implants, owing to the residual monomer catalyzed PLGA hydrolysis. In addition, the drug release profiles were also influenced by other factors, such as polymer-drug interaction and drug solubilities.

### 4. Discussion




All three case studies revealed that the residual monomer considerably accelerated the degradation of the implant and impaired the implant's integrity, which could negatively affect the subsequent drug release behavior and performance of the implant.

A. Dexamethasone implants prepared with Viatel™ ultrapure PLGA maintained the original structure (rigid rod without curvature) for 56 days.

B. Carbamazepine implants prepared with Viatel™ ultrapure PLGA showed delayed disintegration.

C. Morphological observations of the implant's internal structures throughout the dissolution process confirmed that the implant with Viatel™ PLGA degraded faster via a bulk erosion mechanism.

D. Implants with Viatel™ PLGA degraded faster, evidenced by a faster decrease in molecular weights than the implants with Viatel™ ultrapure PLGA. Based on fitting, the degradation time constant decreased from 56.2 days to 35 days, as the residual monomer increased.

## CONCLUSIONS

Polymer characteristics and quality are critical to the stability and performance of PLGA-based drug-loaded implants. New Viatel™ bioresorbable polymers with supreme quality and purity open the door for optimal and innovative implant-based drug delivery systems.

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