M1030-11-73

Manufacturing and elucidating the drug release mechanisms of long-acting ethylene vinyl acetate-based implants

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PURPOSE

The advantages of ethylene vinyl acetate (EVA)-based long-acting implants for drug delivery include improved patient compliance, efficacy, and safety [1]. These complex dosage forms contain dispersed and dissolved drug in a polymeric core coupled with a rate-controlling skin layer. Drug must first dissolve in order to release by diffusion. Release is complex due to presence of dispersed and dissolved drug and a skin layer on the implant length but not the ends. The purpose of this study is to elucidate the release mechanisms of long-acting, EVA-based dispersed-drug implants to support rational design of future polymeric implant systems based on transport properties and development of regulatory guidance for generic drugs.

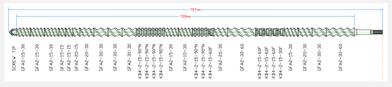
OBJECTIVE(S)

- To manufacture EVA-based subdermal etonogestrel implants
- To elucidate implant release mechanisms and correlate drug release with measured transport properties
- To determine the impact of storage time on drug release
- To characterize physicochemical changes that occur during manufacturing and storage and correlate to release mechanisms

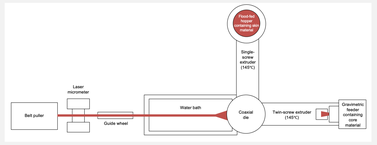
METHOD(S)

Figure 1. Summary of implant manufacturing process.

1(a) Twin-screw profile



1(b) Manufacturing setup

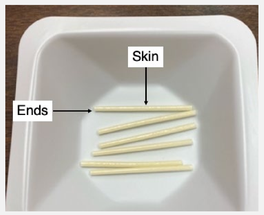


Implants were manufactured using a single coextrusion whose setup consisted of an 18 mm twin-screw and single-screw extruder connected to a die head, water bath, laser micrometer, and puller. The core comprised 30% etonogestrel loaded in EVA 28 and skin was EVA 15 (70 μm). Each implant was 2 mm in diameter, 4 cm long, and contained 38 mg drug. Drug release was measured using an incubator shaker at 37°C and 150 rpm. Release media was 0.00075% Tween 80 in water. Whole implant (skin and ends) release was evaluated using 4 cm long segments. Skin or ends release was measured using 2 cm long segments with desired sections sealed with glue impermeable to etonogestrel. Neat implants were sectioned using a cryostat and visualized using polarized light microscopy. Neat implants were frozen in liquid nitrogen prior to cutting sections for scanning electron microscopy. Partially depleted implants were sectioned using a cryostat and visualized using scanning electron microscopy (SEM). X-ray microcomputed tomography (microCT) was used to investigate the implant microstructure after release. Depleted implants were scanned to obtain an image stack of 963 slices with 0.7 mm x 0.7 mm x 0.7 mm field of view and 0.7 μm resolution. Scans were centered on the implant core. Image segmentation and 3D reconstruction were performed using Dragonfly.

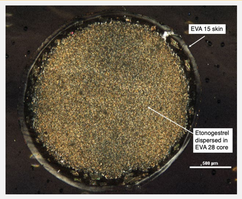
RESULT(S)

Figure 2. Visual characterization of etonogestrel implants.

2(a) Photo of whole implant



2(b) Polarized light microscope (PLM) image of implant cross section



2(c) SEM image of dispersed-drug implant core

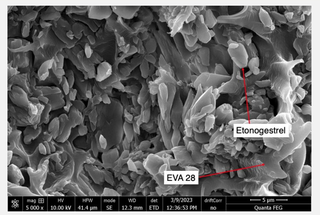
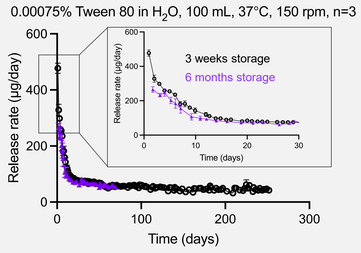
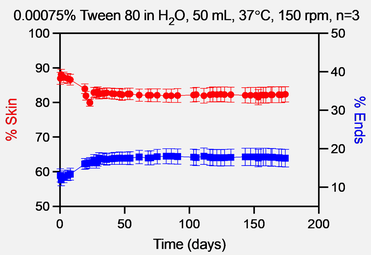


Figure 3. Summary of real-time release behavior from implants. Data points and error bars respectively represent the mean and standard deviation of n=3 replicates.

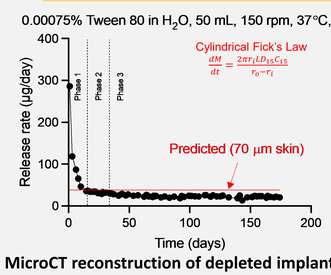
3(a) Impact of storage time at ambient on burst release from whole implant



3(b) Contribution of skin and ends to total release



3(c) Actual versus predicted release from skin



3(d) Actual versus predicted release from ends

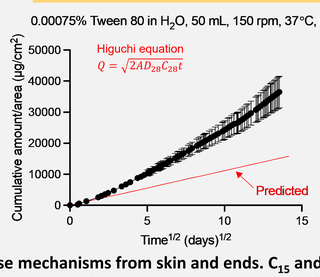
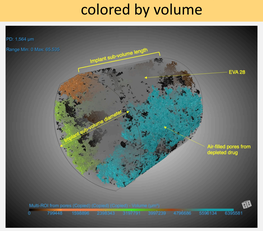
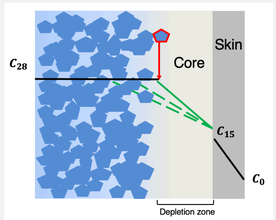


Figure 4. MicroCT reconstruction of depleted implant core and drug release mechanisms from skin and ends. C_{15} and C_{28} represent etonogestrel solubility in EVA 15 and EVA 28, respectively. C_0 represents etonogestrel concentration in release media.

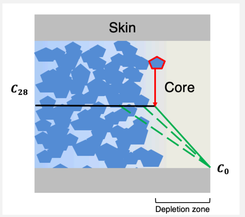
4(a) 3D reconstruction of depleted implant with pores colored by volume



4(b) Drug release mechanism from skin



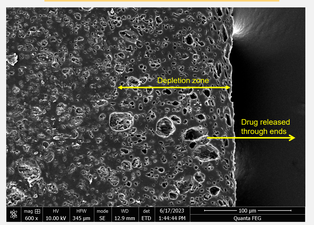
4(c) Drug release mechanism from ends



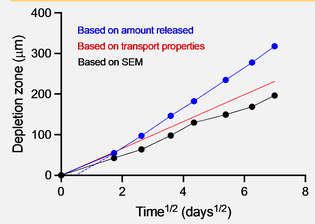
RESULT(S)

Figure 5. Evaluation of solid drug depletion zone in implant core using SEM and amount released.

5(a) SEM image of depletion zone



5(b) Comparison of measured, actual, and predicted depletion zone [2]



CONCLUSION(S)

- Skin release from dispersed-drug EVA-based implants is governed by the ratio of drug dissolution rate/diffusion rate in EVA. When drug cannot dissolve in EVA rapidly enough to maintain the saturation at the core-skin interface, release is dissolution limited [3].
- The initial burst release through skin is due to (1) supersaturation in both skin and core and (2) release of ½ of drug dissolved in the skin. Initial burst is reduced with storage as supersaturated drug recrystallizes in the implant core (Figure 3(a)).
- Skin release occurs in three phases: 1) initial burst 2) steady-state and 3) deviation from steady-state due to formation of a depletion layer which increases diffusion path length (Figure 3(c)).
- Ends release deviates from predicted (Figure 3(d)) due to delayed formation of the depletion zone (Figure 5(b)) and percolating drug domains which increase release rate (Figure 4(a)).
- Percolation can be addressed by employing double extrusion. Optimization of the manufacturing process is critical to ensure uniform drug dispersion [4].

FUNDING & ACKNOWLEDGEMENTS

This work was supported by the Broad Agency Announcement (BAA) Contract # 75F40122C00019 from the U.S. Food and Drug Administration (FDA). The poster reflects the views of the authors and should not be construed to present FDA's views or policies. The authors would like to thank Mark Costello (UT Austin) for his valuable expertise in analyzing microCT data. The authors thank Celanese (Irving, TX) for supplying EVA for this study. The authors would also like to thank the University of Texas High-Resolution X-ray CT Facility for their support in collecting and processing microCT images (NSF EAR-1762458 and 80NSSC23K0199).

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