M1430-11-76

Understanding the impact of accelerated release testing conditions on transport properties and release mechanisms of drug from long-acting ethylene vinyl acetate implants

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PURPOSE

Ethylene vinyl acetate (EVA)-based long-acting reservoir implants such as Nexplanon etonogestrel implant consist of a dispersed drug-containing EVA polymer core and an EVA polymer skin layer. Drug release can be controlled based on material transport properties and implant dimensions. The general release mechanism is based on diffusion, however since the skin layer does not cover the ends, the impact of drug dissolution on release through ends and skin are different. Such implants are designed to deliver drug over multiple years, necessitating accelerated release test methods to facilitate reasonable development times and product release testing. The purpose of this study is to elucidate the impact of accelerated conditions on drug release from dispersed-drug EVA-based implants.

OBJECTIVE(S)

- To evaluate the impact of organic solvent and elevated temperature on transport properties of drug in polymer
- To evaluate the impact of organic solvent and elevated temperature melting behavior and crystalline structure of EVA
- To elucidate the impact of accelerated media on release mechanisms from whole implant, skin only, and ends only

METHOD(S)

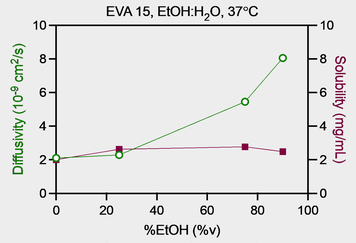
EVA 15 (15% vinyl acetate) films (79 μm thickness) were manufactured using a single-screw extruder fitted with a sheet die and film puller. Etonogestrel solubility in EVA 15 was measured by saturation experiments. Diffusivity was determined using side-by-side diffusion cells. To study the impact of solvent, different compositions of EtOH:H_2O were used at 37°C. To study the impact of temperature, 0.00075% Tween 80 in H_2O was used while temperature was varied. Drug content was assayed using HPLC. Films were stored at elevated temperatures for 12 hours or in 75:25 EtOH:H_2O for 3 weeks, and crystal structure was assessed using differential scanning calorimetry. Degree of swelling (DS) in the presence of organic solvent was assessed by measuring weight gain of EVA 15 films soaked in EtOH:H_2O.

Implants were manufactured using a coextrusion process consisting of a single-screw extruder and a twin-screw extruder combined with a water bath, laser micrometer, and puller. The core and skin are made of EVA 28 and EVA 15, respectively. The core contained 30% drug with most present as solid particles and a low fraction as dissolved in the EVA matrix. Release was conducted using an incubator shaker at 37°C and 150 rpm. To analyze release through ends only (2 cm long) or skin only (2 cm long), implants were sealed with Loctite 4011 glue which is impermeable to etonogestrel. Real-time and accelerated release were conducted in 0.00075% Tween 80 in H_2O and 90:10 EtOH:H_2O, respectively. The accelerated media was selected based Nexplanon test methods, a contraceptive implant with similar release behavior [1].

RESULT(S)

Figure 1. Impact of organic solvent content and temperature on transport properties of etonogestrel in EVA 15 as determined by side-by-side diffusion cells.

1(a) Impact of organic solvent content on transport properties



1(b) Impact of temperature on transport properties [2]

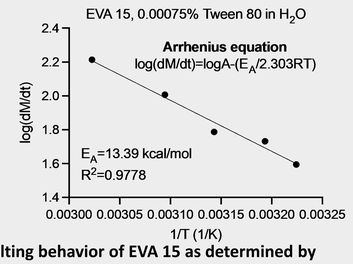
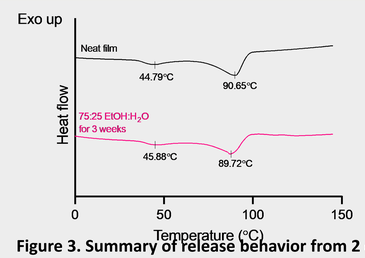


Figure 2. Impact of organic solvent and temperature on melting behavior of EVA 15 as determined by differential scanning calorimetry (DSC).

2(a) Impact of organic solvent on melting and crystal structure



2(b) Impact of temperature on melting and crystal structure

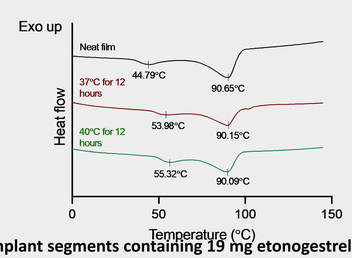
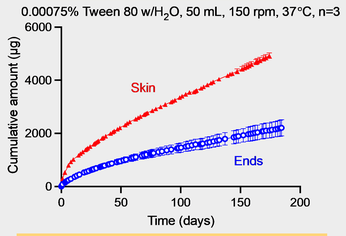
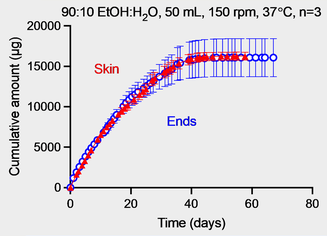


Figure 3. Summary of release behavior from 2 cm long implant segments containing 19 mg etonogestrel. Data points and error bars respectively represent the mean and standard deviation of n=3 replicates.

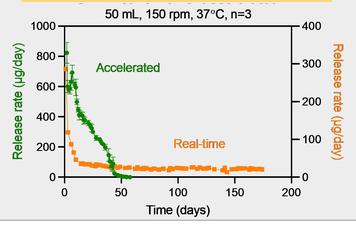
3(a) Ends versus skin: real-time release



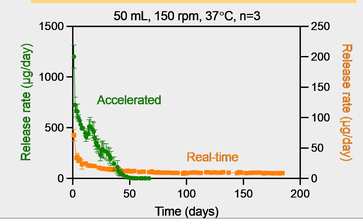
3(b) Ends versus skin: accelerated release



3(c) Skin: real-time versus accelerated release



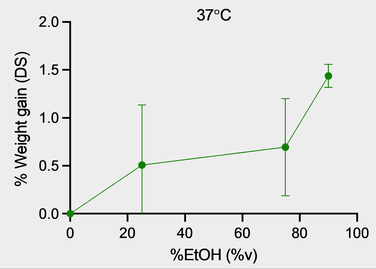
3(d) Ends: real-time versus accelerated release



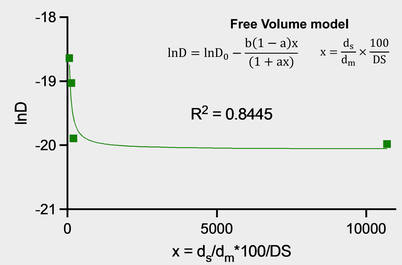
RESULT(S)

Figure 4. EVA 15 degree of swelling in the presence of organic solvent and impact on diffusivity. Data points and error bars respectively represent the mean and standard deviation of n=3 replicates.

4(a) Impact of organic solvent content on degree of swelling



4(b) Correlation of degree of swelling to diffusivity based on the free volume model [3]



CONCLUSION(S)

- Drug release rate increases with temperature and fits the Arrhenius equation (Figure 1(b)), however elevated temperature causes changes in EVA structure due to rearrangement of amorphous and crystalline domains (Figure 2(b)).
- Ethanol had no impact on EVA crystal structure (Figure 2(a)) but caused swelling which increases drug diffusivity by increasing EVA free volume (Figures 4(a) and 4(b)).
- Ethanol increases drug permeability primarily by increasing diffusivity rather than solubility (Figure 1(a)).
- Accelerated release based on organic solvent maintains a diffusion-based mechanism but changes the driving force for release from dispersed-drug implants by changing the drug dissolution rate/diffusion rate ratio in EVA (Figures 3(a)–3(d)).

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 Celanese (Irving, TX) for providing EVA for this study.

REFERENCES

[1] Drugs@FDA. Implanon-clinical pharmacology and biopharmaceutics reviews. FDA. 2006.
[2] Kalachandra, S, Takamata, T, Lin, D.M., Snyder, E.A., Webster-Cyriaque, J. Stability and release of antiviral drugs from ethylene vinyl acetate (EVA) copolymer. Journal of Material Science Materials in Medicine. 2006;17(12).
[3] Chen, S. Diffusion of benzocaine in poly(ethylene-vinyl acetate) membranes: Effects of vehicle ethanol concentration and membrane vinyl acetate content. Journal of Controlled Release. 1995; 38(2-3).