Determination of Drug Crystallinity in Hot Melt Extruded Ethylene Vinyl Acetate Copolymer

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Introduction

Certain methods used to create controlled release delivery systems, such as hot melt extrusion (HME), can potentially impact the physical nature of the incorporated drug(s). The evaluation of the solid physical state (amorphous, crystalline, or partially amorphous) of extrudates provides important information on product drug dissolution, stability, and propensity to crystallization.[1] In this study, FT-Raman spectroscopy was used to determine the relative amounts of crystalline and amorphous (dispersed) progesterone (P) or 17β-estradiol (E2) in ethylene vinyl acetate copolymer (EVA) at various drug loadings.

Methods

Following HME using a single screw extruder, 5 mm diameter fibers containing P or E2 at various concentrations ranging from 5 to 27% (P) and 0.3 to 10% (E2) in EVA (28% VA content) were prepared. The fibers were cut using a razor blade. Raman maps were acquired using a x100 objective (lateral resolution: 1-2 µm). Each map covered 200 x 200 µm with 100 x 100 pixels (i.e., 1 pixel represented 2 µm). Each pixel was acquired over 0.05 sec. Spectra were extracted from Raman maps following a cluster analysis to identify and locate different chemical species. Reference spectra of EVA, P, and E2 were also collected. An example Raman image for 10% P in EVA is shown in Figure 1.

Results

Independent reference spectra of EVA, P and E2 were obtained as described above. A peak at 1680 cm^{-1} was assigned to molecularly dispersed P at in EVA (crystalline P did not have a peak at this wavelength). There is no peak for EVA near this wavelength (see Figure 2). There is a peak at 1662 cm^{-1} (after normalization against the polymer peak at 1738 cm^{-1}) for crystalline P. Using concentrations of P ranging from 5% to 27% in EVA showed that up to 5% P is molecularly dispersed. At higher concentrations, P is found to be crystalline based on the peak at 1662 cm^{-1}. A similar analysis for E2 in EVA indicated that 547 cm^{-1} was appropriate for determining the concentration of crystalline and molecularly dispersed (see Figure 3). This analysis indicated that the amount of molecularly dispersed E2 is <1%.

Conclusions/Implications

The results of this work suggest that FT-Raman spectroscopy can be used to identify molecularly dispersed and crystalline P and E2 in 28% VA content EVA. This technique can be used to assess the physical state of these two drugs following manufacture and over time (e.g., during stability studies).

References

1. R. Censi, *et al.,* Hot melt extrusion: Highlighting physicochemical factors to be investigated while designing and optimizing a hot melt extrusion process. *Pharmaceutics* **10**, 89 (2018)

Acknowledgement

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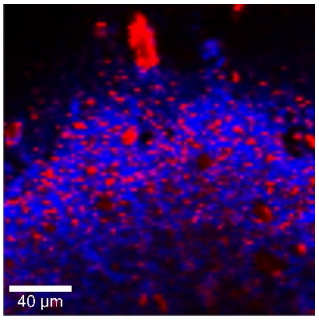

Figure 1. Example Raman image (10% P in EVA)

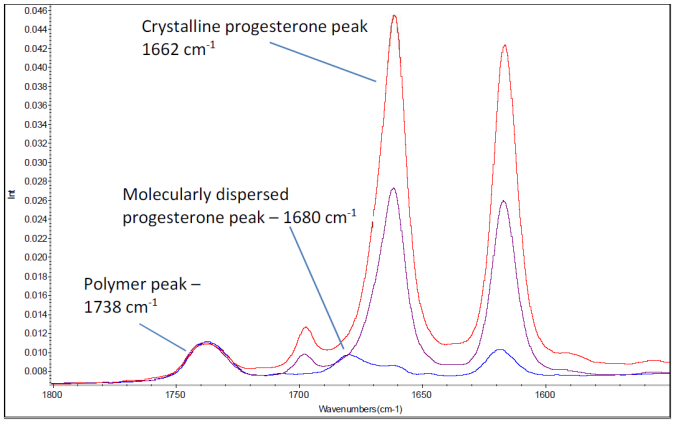

Figure 2. FT-Raman spectra of EVA/P extrudates containing 5% P (blue curve), 15% P (purple curve) and 27% P (red curve) between 1800 and 1500 cm^{-1}.

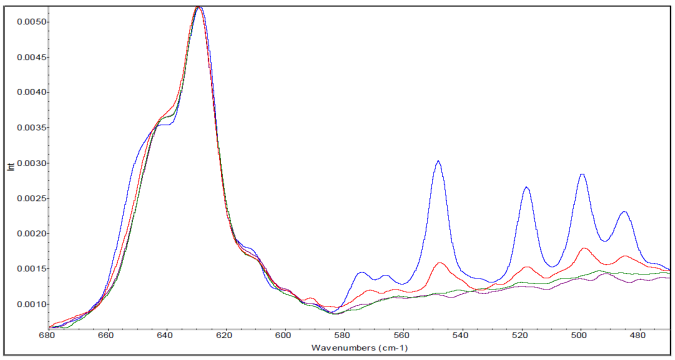

Figure 3. FT-Raman spectra for placebo (purple curve) and EVA/E2 extrudates containing 0.3% (green curve), 2.5% E2 (red curve), or 10% E2 (blue curve) between 680 and 470 cm^{-1}.