Use of FT-Raman Spectroscopy to Assess 17β-Estradiol/ Progesterone Ethylene Vinyl Acetate based Intravaginal Rings

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Introduction

Hot melt extrusion (HME), can potentially impact the physical nature of the incorporated drug(s) in controlled release products. In this study, FT-Raman spectroscopy was used to determine the relative amounts of crystalline 17β-estradiol (E2) and progesterone (P) in EVA-based segmented intravaginal rings (IVRs) at the time of manufacture and after storage (1 and 3 months).

Methods

Following HME using a single screw extruder, 5 mm diameter fibers containing E2 (10 wt%) or P (27 wt%) in EVA (28% VA content) were prepared. Fibers (segments) were heat-sealed to create IVRs capable of releasing 80 µg/d E2 and 4 mg/d P (80/4 IVR) or 160 µg/d and 8 mg P/d (160/8 IVR) through variation in segment length. The appropriate section of the IVRs were cut using a razor blade. Samples for FT-Raman spectroscopy were collected at time of manufacture (t = 0) and at 1, 3 and 6 months following storage at 5°C ambient or 25°C/60% relative humidity (RH). 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 different chemical species. Previous work indicated that the amount of dispersed (amorphous) E2 and P was <1% and 5%, respectively.

Results

A peak at 547 cm^{-1} was used to determine the concentration of crystalline E2 in EVA; data from this wavelength was normalized against a peak from EVA at 1738 cm^{-1}. Likewise, a peak at 1662 cm^{-1} was assigned to crystalline P with normalization to the same EVA peak (1738 cm^{-1}). The normalized peak intensity at 547 cm^{-1} (E2) at t = 0 was 0.21 from both the 80/4 and the 160/8 IVRs. This value remained at 0.21 or 0.20 over 1, 3 and 6 months at both storage conditions. For P, the normalized peak at 1662 cm^{-1} at t = 0 was 11.8 (80/4 IVR) and 12.1 (160/8 IVR). These values fluctuated slightly at 1, 3 and 6 months storage conditions but with no apparent change. The data are summarized in Table 1.

Conclusions/Implications

These data are consistent with additional characterization, and demonstrate no measurable change in the amount crystalline E2 and P in the 80/4 and 160/8 IVRs under the tested storage conditions. These results confirm that FT-Raman can be an effective analytical tool to assess drug stability in IVRs.[1]

Reference

1. Bell et al., *J. Pharm. Pharmacol.*, **59**: 203-207 (2007)

Acknowledgement

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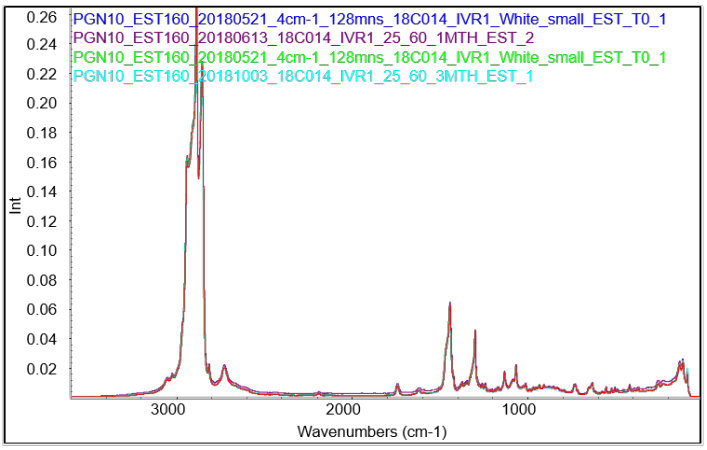

Figure 1. Raman spectra of E2 at t = 0, 1, 3 and 6 months stored at 25°C/60% RH from the 160/8 IVR

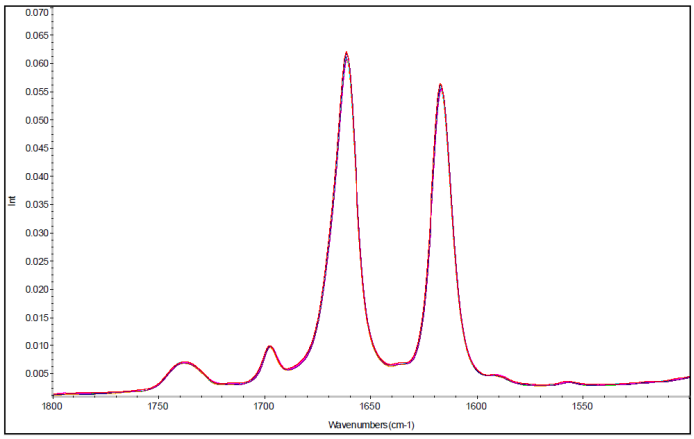

Figure 2. Raman spectra of P at t = 0, 1, 3 and 6 months stored at 25°C/60% RH from the 160/8 IVR

Table 1. Normalized peak intensity for E2 (547 cm^{-1}) and P (1662 cm^{-1}) at t = 0, 1, 3, and 6 months storage at 25°C/65% RH)

Time	E2 Peak		P Peak	
	80/4 IVR	160/8 IVR	80/4 IVR	160/8 IVR
T = 0	0.21 ± 0.005[a]	0.21 ± 0.005	11.8 ± 0.21	12.1 ± 0.21
T = 1 mon	0.20 ± 0.006	0.20 ± 0.006	11.8 ± 0.17	12.1 ± 0.27
T = 3 mon	0.21 ± 0.007	0.21 ± 0.007	11.7 ± 0.17	12.0 ± 0.21
T = 6 mon	0.21 ± 0.007	0.20 ± 0.006	11.9 ± 0.14	11.8 ± 0.14

[a]Data are means ± SD (*n* = 3)