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Evaluation of Different Suppliers of Ethylene Vinyl Acetate Used in Intravaginal Rings

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PURPOSE

To evaluate ethylene vinyl acetate (EVA) copolymer from three different suppliers used to prepare segmented intravaginal rings (IVRs) for the sustained release of estradiol (E_2) and progesterone (P). This rings is designed to provide hormone therapy to treat vasomotor symptoms in post-menopausal women.

OBJECTIVES

1) Prepare segmented E_2 and P IVRs with 28% vinyl acetate content EVA from three different suppliers.
2) Compare in vitro release rates and mechanical properties

METHODS

Rings were prepared by blending milled EVA powder with either E_2 or P followed by hot melt extrusion using a twin-screw extruder and cutting the resulting strands into small pieces. The drug-containing EVA pieces were coated with a small amount of lubricant (magnesium stearate) and extruded using a single screw extruder to create segments. Segments were loaded with 10% E_2 or 27% P. Segment lengths were cut to provide release of the desired release of E_2 of 160 µg/d and P at 8 mg/d (160/8 IVR). Similar silicone-based IVRs releasing these two drugs with these approximate release rates have been found to be effective in treatment of vasomotor symptoms in post-menopausal women. Rings (5 mm x 57mm) were prepared by welding the appropriate segments. The finished rings were inspected visually. The rings were evaluated for their mechanical properties by measuring maximum force and distance at maximum force, and the same for force at break. Compression testing(force required to compress rings 5 and 30 mm in two different orientations) of the IVRs was also conducted. The release of both drugs from the IVRs prepared with the EVA from the three different suppliers was measured over a 28-day period. All these tests were conducted at the time of manufacture and following 3 months storage stability at 30°C/65% relative humidity (rh). All measures were conducted with 6 replicates.

RESULTS

There were no visual differences noted between the rings prepared with EVA from the three different suppliers. Overall, a comparison of the mechanical results found very similar results when evaluating the IVRs prepared from the three different sources of EVA. For instance, the force at break (kg) for the three IVRs were 15.8 ± 0.38, 14.1 ± 0.41, and 13.1 ± 0.32 and the distance at break (mm) was 208 ± 69.5, 271 ± 104, and 158 ± 62.1, for rings made with EVA1, EVA2, and EVA3, respectively. The force (N) required to compress the rings 5 mm in two different orientations (relative to the E_2 segment) were 1.59 ± 0.14, 1.53 ± 0.04, and 1.84 ± 0.10 (orientation 1) and 1.63 ± 0.10, 1.56 ± 0.01, and 1.79 ± 0.09 (orientation 2) for rings made with EVA1, EVA2, and EVA3, respectively.

Dissolution testing (200 mL 0.5% sodium dodecyl sulfate shaken at 130 ± 2 rpm) was conducted on the rings to assess daily release rates of both E_2 and P over 28 days. Release rates were those expected from matrix devices as shown in Fig. 1 (E_2 daily release) and Fig. 2 (P daily release). The release of E_2 from rings prepared with EVA from the three different suppliers were nearly identical with a slight difference seen at Day 1. The release of E_2 determines the effectiveness of these products in alleviating vasomotor symptoms (VMS) so it is important that the release rates show minimal differences. The release of P from these same rings was similar to that of E_2 but showed slightly more variability although differences were most pronounced over the first several days of the release study. All these tests were repeated following 3 months of storage at 30°C/65% rh. There were no meaningful differences noted between the results when compared with the data collected following ring manufacture.

CONCLUSIONS

These data support the conclusion that EVA (28% VA content) from the three different suppliers can be used to prepare IVRs capable of the controlled release of E_2 and P. While there were some minor differences between the EVA used (one EVA had a lower melt-flow index than the other two sources) there was remarkable consistency in the results obtained.

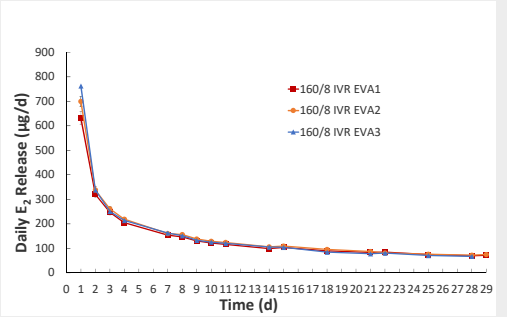

Fig. 1. Dissolution of E_2 from segmented IVRs (160/80) prepared from 28% vinyl acetate content EVA from three different suppliers.

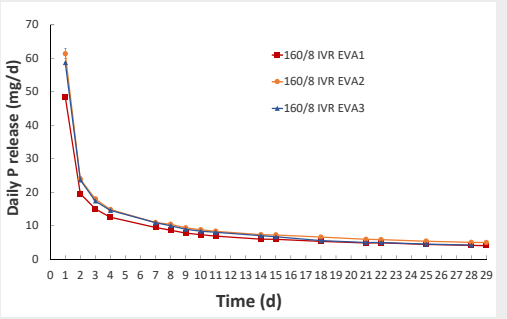

Fig. 2. Dissolution of P from segmented IVRs (160/80) prepared from 28% vinyl acetate content EVA from three different suppliers.

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