Impact of Particle Size and Release Testing Media on Release of Dapivirine from a Silicone Elastomer Vaginal Ring

Impact of Particle Size and Release Testing Media on Release of Dapivirine from a Silicone Elastomer Vaginal Ring

Diarmaid J. Murphy¹, Clare F. McCoy¹, Peter Boyd¹, Tiffany Derrick², Pat Spence², Brid Devlin², R. Karl Malcolm¹

Key points
1. Particle size is a critical parameter in dosage form designs containing solid drugs due to its impact on the rate of drug dissolution.
2. Micronised and non-micronised DPV rings displayed considerable variation in release rates within the same release media. Release was 1.5–3 times faster from rings containing micronised drug.
3. Both release media were able to easily distinguish between rings containing micronised vs non-micronised drug. IPA+water provided better discrimination at earlier time points while SVF+Tween provided good discrimination at later time points.

Background
Drug particle size is often a critical formulation parameter in the design of delivery systems containing solid drugs due to its influence on the rate of drug dissolution. Surprisingly, the impact of drug particle size has not previously been reported for drug-releasing vaginal rings. Here, we report the impact of dapivirine (DPV) particle size (non-micronised versus micronised) on in vitro release from the International Partnership for Microbicides’ 25 mg DPV vaginal ring using two different release media.

Objectives
1. Manufacture 25 mg DPV rings using both non-micronised and micronised drug powder.
2. Measure drug loading and drug distribution by ring content analysis.
3. Assess effect of drug particle size on the in vitro release of DPV into a 1:1 (v/v) mixture of isopropanol (IPA) and water (IPA+water) and simulated vaginal fluid containing 0.2% w/v Tween 80 (SVF+Tween).

Methods
Matrix-type, silicone elastomer vaginal rings containing 25 mg of either non-micronised (D₉₀, 19 µm; D₅₀, 101 µm; D₁₀, 302 µm) or micronised (D₉₀, 2 µm; D₅₀, 5.9 µm; D₁₀, 14 µm) DPV were manufactured by reaction injection molding on a Babyplast 6/10P. The DPV content per ring was established through acetone extraction of sectioned rings and quantification of drug using HPLC. Comparative in vitro release of DPV from rings was assessed over 28 days in an orbital shaking incubator (37°C, 60 rpm) using two different dissolution media – IPA+water and SVF+Tween. Release media were completely replaced daily with larger volumes used over weekends. DPV concentrations were quantified by HPLC.

Results & Discussion
Daily in vitro release versus time profiles for DPV release from rings containing micronised and non-micronised drug is displayed in Fig. 1. Cumulative release profiles are displayed in Fig. 2.

Rings containing micronised DPV had an off-white opaque appearance whereas rings containing non-micronised drug were translucent with visible drug particles dispersed throughout. Content analysis of 12 rings from each ring formulation gave mean DPV loadings per ring of 25.4 and 24.8 mg for non-micronised and micronised drug, respectively.

Daily and cumulative release profiles (Figs. 1 and 2) for rings containing different particle sizes of DPV show trends typical of permeation controlled release from matrix-type devices into both release media. DPV release rates into IPA+water were significantly greater than those in SVF+Tween as expected on the basis of DPV solubility in the two release media (Table 1). Similarly, release rates for rings containing micronised DPV were significantly greater than those measured from rings containing non-micronised drug into both release media (Table 1). These differences can be attributed to differences in the rate of drug dissolution in the silicone elastomer prior to diffusion through the ring. The daily release profiles show that both release media are able to discriminate between rings manufactured with different particle size distributions of DPV. IPA+water showed greater discrimination at earlier time points while SVF+Tween showed greater discrimination at later time points.

Table 1. Cumulative release profile line gradients and coefficients of determination

<table>
<thead>
<tr>
<th>Ring Type</th>
<th>Release media</th>
<th>Release rate (95% CI; µg/day)</th>
<th>r² value</th>
</tr>
</thead>
<tbody>
<tr>
<td>nm-DPV</td>
<td>IPA+water</td>
<td>1450 (1421, 1479)</td>
<td>0.9983</td>
</tr>
<tr>
<td>m-DPV</td>
<td>IPA+water</td>
<td>2175 (2126, 2224)</td>
<td>0.9978</td>
</tr>
<tr>
<td>nm-DPV</td>
<td>SVF+Tween</td>
<td>322 (315, 330)</td>
<td>0.9977</td>
</tr>
<tr>
<td>m-DPV</td>
<td>SVF+Tween</td>
<td>949 (925, 974)</td>
<td>0.9871</td>
</tr>
</tbody>
</table>