Objective

Drug release testing of low-dose extended release (ER) dosage forms requires precise, standardized and validated methods. In this study the applicability of USP apparatus 7, the reciprocating holder (USP 7), to determine in vitro etonogestrel (ENG) release from an intravaginal ring (IVR) under both real-time and accelerated test conditions was investigated. NuvaRing® was chosen as a model formulation. Results from USP 7 release experiments were compared with those of release experiments performed in a miniaturized “hanging sinker” setup and with published release profiles for NuvaRing® that resulted in an IVIC [1,2].

Methods

- Capped segments (1-1.5 cm) were used instead of entire rings
  - Release from one IVR was calculated based on the mass ratio
- Two different experimental setups were used:
  - USP 7-400-DS (Agilent Technologies)
    - Dip rate: 40 rpm
    - Volume of release medium: 10 mL
    - Automated sampling as well as media replacement were performed every 12 h
  - Miniaturized “hanging sinker” setup
    - Stirring Speed: 100 rpm
    - Volume of release medium: 25 mL
    - Manual sampling as well as media replacement were performed daily (with exceptions)
- Real-time conditions:
  - Temperature: 37 °C
  - Release Medium: Vaginal fluid simulant (VFS) [3]
- Accelerated conditions:
  - A) Temperature: 50 °C
  - B) Release medium: 50 % EtOH (V/V)
  - adjusted intervals for sampling and media replacement
- Quantification:
  - HPLC-UV-VIS (242 nm)
    - Column: RP-18 4.6 x 150 mm 5 μm
    - Mobile Phase: 75/25 MeOH/H₂O, Flow rate: 1 mL/min

Table 1: Standard in vitro release method for NuvaRing® [1]

<table>
<thead>
<tr>
<th>Apparatus</th>
<th>Automated release control system</th>
<th>Automated release control system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium</td>
<td>Ultrapure water</td>
<td>Ultrapure water</td>
</tr>
<tr>
<td>Volume</td>
<td>200 mL</td>
<td>200 mL</td>
</tr>
<tr>
<td>Temperature</td>
<td>37 °C</td>
<td>37 °C</td>
</tr>
<tr>
<td>Stirring Speed</td>
<td>370 rpm</td>
<td>370 rpm</td>
</tr>
<tr>
<td>Sampling Times</td>
<td>Daily</td>
<td>Daily</td>
</tr>
<tr>
<td>Sampling Volume</td>
<td>200 mL</td>
<td>200 mL</td>
</tr>
</tbody>
</table>

NuvaRing® is a combined hormonal contraceptive IVR made of polyethylene vinylacetate copolymer that releases 120 μg ENG and 15 μg ethinylestradiol daily over three weeks. FDA approved standard test conditions for NuvaRing® are given in Table 1. For both drugs a level A IVIC was successfully established [1,2].

Results

Real-time release:

Comparison with published release profiles for NuvaRing® obtained under standard test conditions [1] (Table 1)

ENG release in USP 7 was lower than under standard test conditions and in the miniaturized “hanging sinker” setup.

The changes in the daily release profile over time are well reflected. Similar trend with time!

Accelerated release (Temperature): The sampling frequency was adjusted to reflect daily real-time release

Acclerated release (Hydro-alcoholic mixtures)

Correlation between real-time and accelerated release

Hydroalcoholic media vs. temperature

* scaling factor: k scaling = k real-time / k accelerated

Fig. 1: Daily ENG release from ring segments in the miniaturized setup and in USP 7 standardized to release per ring at 37 °C. Mean ± SD. n = 3.

A published ENG release profile from NuvaRing® under standard test conditions is plotted in the same graph [1].

Fig. 2: Daily ENG release from ring segments in USP 7 at 37 °C and 50 °C with adjusted sampling frequencies standardized to release per ring. Mean ± SD. n = 3.

Fig. 3: Daily ENG release from ring segments at 37 °C and 50 °C after time scaling (scaling factor 4.79) standardized to release per ring. Mean ± SD. n = 3.

Conclusion

The USP 7 method proved to be both precise and sensitive under real-time and temperature-controlled accelerated test conditions. Due to the different hydrodynamic conditions in the two setups drug release in USP 7 was somewhat lower than under standard test conditions. However, the release profiles obtained under FDA-approved standard test conditions and in USP 7 show a similar trend with time. Elevated temperature release experiments with adjusted sampling frequencies were found to be predictive of real-time release in both setups. As a result of the more precise temperature control in USP7 an even stronger correlation was seen for this setup. Drug release in hydro-alcoholic mixtures increased with alcohol content (not shown) but compared with elevated temperature experiments initial experiments in EtOH 50 % indicated a lower sensitivity in monitoring the changes in real-time release over time. Overall, the results demonstrate that USP 7 is a useful tool for long-term and accelerated release studies of low-dose ER formulations.

Acknowledgement:

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References:

3. Owen DH, Katz DP. Contraception. 1990, 50 (2) 01-05.