Application of USP apparatus 7 in Performing Real Time and Accelerated Release Studies of an Intravaginal Ring

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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 IVIVC [1,2].

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

Apparatus	Automated release control system
Medium:	Ultrapure water
Volume	200 mL
Temperature	37 °C
Stirring Speed	750 rpm
Sampling Times:	Daily
Sampling Volume:	200 mL

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 IVIVC was successfully established [1,2].

Methods

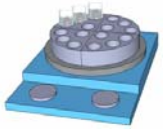
- Endcapped segments (1-1.5 cm) were used instead of entire rings
  → Release from one IVR was calculated based on the mass ratio

➢ *Two different experimental setups were used:*

USP 7 400-DS (Agilent Technologies)

- Dip rate: 40 dpm
- 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: 20 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/H_2O, Flow rate: 1 mL/min

Results

Real-time release:

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

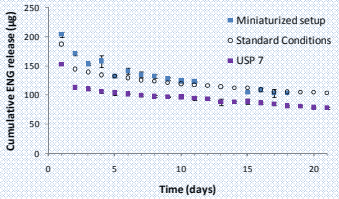


Fig. 1: Daily ENG release from ring segments in the miniaturized setup and in USP 7 standardized to release per ring at 37 °C. Mean ± SD; n = 3. A published ENG release profile from NuvaRing® under standard test conditions is plotted in the same graph [1].

→ 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

$$t(h)\uparrow = \frac{k_{37\,°C} \cdot 24\,h}{k\uparrow}$$

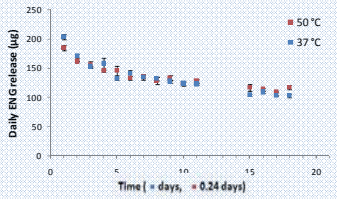


Fig. 2: Daily ENG release from ring segments in the miniaturized setup at 37 °C and 50 °C with adjusted sampling frequencies standardized to release per ring. Mean ± SD; n = 3.

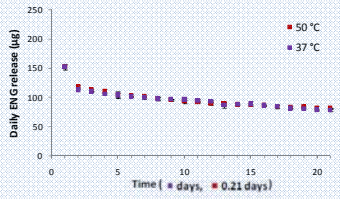


Fig. 3: Daily ENG release from ring segments in USP 7 at 37 °C and 50 °C with adjusted sampling frequencies standardized to release per ring. Mean ± SD; n = 3.

Accelerated release (Hydro-alcoholic mixtures)

Correlation between real-time and accelerated release Hydroalcoholic media vs. temperature

$$*\text{scaling factor} = \frac{k_{accelerated}}{k_{real-time}}$$

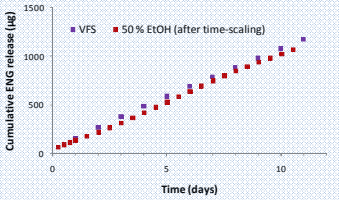


Fig. 4: Cumulative ENG release from ring segments in VFS and EtOH 50 % after time scaling (*scaling factor 6.03) standardized to release per ring. Mean; n=3.

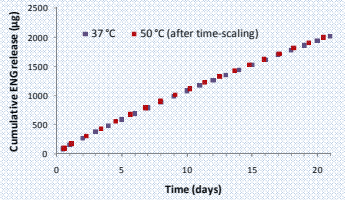


Fig. 5: Cumulative ENG release from ring segments at 37 °C and 50 °C after time scaling (*scaling factor 4.79) standardized to release per ring. Mean; n=3.

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.

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Agilent Technologies

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1. Marroum PJ. Presentation at the XX Pan-American Congress of Pharmacy, FIP Dissolution Workshop, Porto Alegre, Brazil, May 2010.
2. Marroum PJ in: Chilukuri DM, Sunkara G, Young D. Informa Healthcare 2007, New York, 188-192
3. Owen DH, Katz DF. Contraception. 1999, 59 (2):91-95.