Challenges and considerations in the development and validation of *in vitro* drug release testing for intravaginal rings

Karl Malcolm
In vitro release testing methods for drug-releasing vaginal rings

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Content

- Vaginal rings
- The human vagina
- Methods for \textit{in vitro} release testing
- \textit{In vitro-in vivo} correlations (IVIVC)
- Challenges
Vaginal rings

http://www.google.com/patents/US3545439

ABSTRACT: An improved resident annular device for intravaginal placement and retention as required and formed of a compatible nonabsorbable polymeric substance such as an organopolysiloxane, nylon, natural or synthetic rubber, dacron, teflon, polyurethane and polyethylene and containing an effective amount of a medicament which is capable of passage through the drug-permeable polymeric material. The device is useful to provide a readily inserted, readily retained and readily removable source of continued medication for sustained beneficial effects in female mammals, human and animal.
Vaginal rings

First patent


Nuvaring®

Estring®

Sweden

UK

US

US & Europe

Progering®

Fertiring®

Estrin®

Chile

S. America

UK

US

Femring®

Annovera®

Ornibel®

Dapivirine

EU

UK & US

S. America

EU
Thank you for listening!

‘Nuala with the Hula’

A famous Belfast landmark
Vaginal rings

Drug molecules

McBride et al., Vaginal rings with exposed cores for sustained delivery of the HIV CCR5 T inhibitor 5P12-RANTES, Journal of Controlled Release 298 (2019) 1–11
Vaginal rings
Regulatory considerations

- Single entity combination products / as defined in 21 CFR 3.2(e)
- Drug + device
- “For drug delivery vaginal rings, primary mode of action relates to the ‘drug’ component"
Vaginal rings
Drug product specification tests

<table>
<thead>
<tr>
<th>Product quality tests</th>
<th>Product performance tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance and Description</td>
<td><em>In vitro</em> release testing</td>
</tr>
<tr>
<td>Identification</td>
<td></td>
</tr>
<tr>
<td>Assay (drug content)</td>
<td></td>
</tr>
<tr>
<td>Impurities / Related substances / Degradation products</td>
<td></td>
</tr>
<tr>
<td>Uniformity of dosage unit (ring weight)</td>
<td></td>
</tr>
<tr>
<td>Content uniformity</td>
<td></td>
</tr>
<tr>
<td>Microbial limits</td>
<td></td>
</tr>
</tbody>
</table>
Vaginal rings
Mechanical testing

Mechanical testing methods for drug-releasing vaginal rings

Clare F. McCoya, Bronagh G. Millara, Diarmuid J. Murphya, Wendy Blandab, Bashir Hansrajb, Brid Devlinb, R. Karl Malcolmc, Peter Boydab,d

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c School of Mechanical and Aerospace Engineering, Queen’s University Belfast, Belfast BT9 5AH, UK

dArticle Info

Keywords:
ISO
ASTM method
Compression test
Tensile test
Intravaginal ring

Abstract

Vaginal rings (VRs) are currently marketed for contraceptive or hormone regulation purposes, and investigationally, have been widely reported for delivery of antiretrovirals to reduce HIV transmission. To date, there is no national or international standard for the mechanical testing and minimum performance characteristics of any VR based products. Here, we describe a series of mechanical tests examining the durometer hardness, static and dynamic compression response, tensile properties and twist resistance of vaginal rings. The tests were conducted on currently marketed VRs and a number of the International Partnership for Microbicides’ (IPM) investigational VR formulations. With wider application in the field, the tests described herein could form the basis for a more standardised approach to the mechanical testing of VRs.
Content

- Vaginal rings
- The human vagina
- Methods for *in vitro* release testing
- *In vitro-in vivo* correlations
- Challenges
The human vagina

<table>
<thead>
<tr>
<th>Mucosa</th>
<th>Surface area (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>oral</td>
<td>200</td>
</tr>
<tr>
<td>gastrointestinal</td>
<td>350,000</td>
</tr>
<tr>
<td>skin</td>
<td>20,000</td>
</tr>
<tr>
<td>vaginal</td>
<td>90</td>
</tr>
</tbody>
</table>

The human vagina

A Vaginal Fluid Simulant
Derek H. Owen* and David F. Katz*†

A fluid medium was developed to simulate the fluid produced in the human vagina. The composition of the medium was based on an extensive review of the literature on constituents of human vaginal secretions. In choosing the ingredients for this medium, the goal was to emphasize properties that influence interactions of vaginal fluid with topical contraceptive, prophylactic, or therapeutic products. Among these properties, pH and osmolarity play a dominant role in physicochemical processes that govern drug release and distribution. Contraception 1999;59:91–95 © 1999 Elsevier Science Inc. All rights reserved.

Key words: vaginal, fluid, secretions, simulant, composition

Introduction

When therapeutic, contraceptive or prophylactic formulations are applied to the vagina, they encounter a variety of fluids with widely varying physical and chemical properties. Native material originating within the vagina. Vaginal fluid has many properties distinct from those of semen and mucus, and interactions of formulations with this material may be physicochemically different from those with semen or mucus.

Our laboratory has been studying how the deployment and delivery of contraceptive and prophylactic compounds are affected by the properties of the delivery vehicle and its interactions with the surrounding fluids. It was found that the osmolarity and pH of the delivery vehicle and the surrounding fluid are important factors in modulating drug delivery. Osmolarity and pH are also important in determining the rheological properties of many commonly used delivery gels. It is therefore useful to employ a vaginal fluid simulant with physical and chemical properties, particularly pH and osmolarity, that model those of native vaginal fluid. The formula for this simulant was developed after an exhaustive review of the literature.

Owen DH, Katz DF, A vaginal fluid simulant, Contraception, 1999;59(2):91-95.
The human vagina

○ Composition of vaginal fluid
  • salts, proteins, carbohydrates, low molecular weight organic compounds, lactic acid, acetic acid, glycerol, urea, glucose

○ Quantity of vaginal fluid
  • 0.5–0.75 g fluid present at any one time
  • 6 g /day production

○ Vaginal pH
  • 3.5 – 4.5 in healthy, non-menstruating, premenopausal women
  • >4.5 in healthy, post-menopausal women
### The human vagina

Vaginal fluid simulant

<table>
<thead>
<tr>
<th>Component</th>
<th>Concentration (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>3.51</td>
</tr>
<tr>
<td>KOH</td>
<td>1.40</td>
</tr>
<tr>
<td>Ca(OH)$_2$</td>
<td>0.222</td>
</tr>
<tr>
<td>bovine serum albumin</td>
<td>0.018</td>
</tr>
<tr>
<td>lactic acid</td>
<td>2.00</td>
</tr>
<tr>
<td>acetic acid</td>
<td>1.00</td>
</tr>
<tr>
<td>glycerol</td>
<td>0.16</td>
</tr>
<tr>
<td>urea</td>
<td>0.4</td>
</tr>
<tr>
<td>glucose</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Adjust to pH 4.2
The human vagina

Histology

A

En simple columnar

Ec stratified squamous

B

stratified squamous
The human vagina
Drug absorption

1. dissolution
2. diffusion
3. partitioning
4. diffusion
5. partitioning
6. diffusion
Content

- Vaginal rings
- The human vagina
- Methods for *in vitro* release testing
- *In vitro*-in *vivo* correlations
- Challenges
**In vitro release testing**

Factors: Drug / drug product

- ring type (e.g. matrix, reservoir, pod, insert, exposed core, etc.)
- overall ring dimensions
- core length (for reservoir rings)
- membrane thickness (for reservoir rings)
- drug type
- drug solubility in the ring polymer
- drug diffusivity in the ring polymer
- initial drug loading (for matrix rings)
- drug particle size distribution
- salt form of drug
- polymorphic form of drug
- co-formulation / drug-drug interactions
- polymer type and grade
- cure temperature and time (for silicone elastomer)
- molding/extrusion temperature (thermoplastics)
- formulation excipients
- drug photosensitivity
- ring storage / storage conditions
**In vitro** release testing

Factors: Testing parameters

- type of test (shake-flask vs. flow-through)
- type of agitation (orbital vs. linear shaking)
- composition of release medium
- pH of release medium
- volume of release medium
- sink vs non-sink conditions
- sampling frequency and interval
- frequency of medium replacement
- rate of stirring
- rate and diameter of orbital shaking
- temperature of release medium / prewarming of medium
- position of ring in flask (suspended or lying flat)
- type of flask / shape of flask (affects fluid dynamics around the ring)
In vitro release testing

- Ring types
- Release testing equipment
- Release medium type
- Release medium volume
- Shaking speeds
- Release medium sampling schedules
In vitro release testing
Ring type / Matrix rings

- solid crystalline drug dispersed throughout ring volume
- manufacture via one-step injection molding process
- Fertiring®, Progering®, dapivirine ring

In vitro release testing
Ring type / Matrix rings
In vitro release testing

Ring type / Matrix rings / Metronidazole

![Graphs showing daily and cumulative MET release over time for different MET doses (1000 mg, 500 mg, 250 mg, 100 mg).]
In vitro release testing
Matrix rings / Release kinetics

<table>
<thead>
<tr>
<th>Category</th>
<th>Equation</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Classical Higuchi | \[
\frac{M_t}{A} = \sqrt{DC_S (2C_0 - C_S)t}
\] | \(M_t\) – cumulative release, \(A\) – ring surface area, \(D\) – drug diffusion coefficient, \(C_S\) – drug solubility in polymer, \(C_0\) – initial drug conc. in ring, \(t\) – time |
| Simplified Higuchi | \[
\frac{M_t}{A} = \sqrt{DC_S (2C_0)t}
\] | * |
| General form    | \(M_t = k \sqrt{t}\)                        |                                           |

* assumes \(C_0 \gg C_s\)

Siepmann & Peppas, Higuchi equation: Derivation, applications, use and misuse, International Journal of Pharmaceutics 418 (2011) 6–12
In vitro release testing
Ring type / Reservoir rings

- Estring®, Nuvaring®, Femring®, Ornibel®
- solid or dissolved drug dispersed throughout core only
- multi-step injection molding for silicone elastomer rings
- co-extrusion for thermoplastic rings
In vitro release testing

Ring type / Reservoir rings

Time (days)

Daily release (mcg)

Cumulative release (mcg)

B

with burst

with lag

D

with burst

with lag
In vitro release testing
Ring type / Reservoir rings / MPTs

Boyd et al., International Journal of Pharmaceutics 511 (2016) 619–629
### In vitro release testing

Reservoir rings / Release kinetics

<table>
<thead>
<tr>
<th>Equation Type</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crank’s equation</td>
<td>( M_t = \frac{(2\pi C_s D L)}{\ln \frac{b}{a}} t )</td>
</tr>
<tr>
<td>Chien’s equation</td>
<td>( M_t = \frac{(C_s D A)}{h} t )</td>
</tr>
<tr>
<td>General form</td>
<td>( M_t = k t )</td>
</tr>
</tbody>
</table>

- \( M_t \) – cumulative release
- \( A \) – ring surface area
- \( D \) – drug diffusion coefficient
- \( C_s \) – drug solubility in polymer
- \( L \) – length of core
- \( b \) – cross-sectional radius ring
- \( a \) – cross-sectional radius core
- \( h \) – sheath thickness
- \( t \) – time
In vitro release testing
Release testing equipment

Fig. 2. Different type of shaking incubators commonly used for in vitro release testing of vaginal rings. A – a benchtop shaking incubator; B – a floor-standing top-opening orbital shaking incubator; C – stackable orbital shaking incubators; D – flasks containing suspended rings, and stored in an orbital shaking incubator.
**In vitro release testing**

Release medium type

<table>
<thead>
<tr>
<th>Ring</th>
<th>Medium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertiring®</td>
<td>isotonic saline</td>
</tr>
<tr>
<td>Estring®</td>
<td>0.9% saline</td>
</tr>
<tr>
<td>Progering®</td>
<td>isotonic saline</td>
</tr>
<tr>
<td>Nuvaring®</td>
<td>water</td>
</tr>
<tr>
<td>Femring®</td>
<td>0.9% saline</td>
</tr>
<tr>
<td>Ornibel®</td>
<td>pH 4.2 acetate buffer +0.05% Solutol HS 15</td>
</tr>
<tr>
<td>Annovera®</td>
<td>water</td>
</tr>
<tr>
<td>dapivirine</td>
<td>1:1 isopropanol/water</td>
</tr>
</tbody>
</table>
In vitro release testing
Release medium volume

<table>
<thead>
<tr>
<th>Ring</th>
<th>Medium</th>
<th>Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertiring®</td>
<td>isotonic saline</td>
<td>250</td>
</tr>
<tr>
<td>Estrin®</td>
<td>0.9% saline</td>
<td>250</td>
</tr>
<tr>
<td>Progering®</td>
<td>isotonic saline</td>
<td>250</td>
</tr>
<tr>
<td>Nuvaring®</td>
<td>water</td>
<td>200</td>
</tr>
<tr>
<td>Femring®</td>
<td>0.9% saline</td>
<td>500</td>
</tr>
<tr>
<td>Ornibel®</td>
<td>pH 4.2 acetate buffer +0.05% Solutol HS 15</td>
<td>100</td>
</tr>
<tr>
<td>Annovera®</td>
<td>water</td>
<td>400</td>
</tr>
<tr>
<td>Dapivirine</td>
<td>1:1 isopropanol/water</td>
<td>100</td>
</tr>
</tbody>
</table>
**In vitro release testing**

Shaking speeds

<table>
<thead>
<tr>
<th>Ring</th>
<th>Medium</th>
<th>Volume (mL)</th>
<th>Shaking speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertiring®</td>
<td>isotonic saline</td>
<td>250</td>
<td>NA</td>
</tr>
<tr>
<td>Estring®</td>
<td>0.9% saline</td>
<td>250</td>
<td>60/130 rpm</td>
</tr>
<tr>
<td>Progering®</td>
<td>isotonic saline</td>
<td>250</td>
<td>NA</td>
</tr>
<tr>
<td>Nuvaring®</td>
<td>water</td>
<td>200</td>
<td>750 rpm</td>
</tr>
<tr>
<td>Femring®</td>
<td>0.9% saline</td>
<td>500</td>
<td>NA</td>
</tr>
<tr>
<td>Ornibel®</td>
<td>pH 4.2 acetate buffer +0.05% Solutol HS 15</td>
<td>100</td>
<td>60 rpm</td>
</tr>
<tr>
<td>Annovera®</td>
<td>water</td>
<td>400</td>
<td>100 opm</td>
</tr>
<tr>
<td>Dapivirine</td>
<td>1:1 isopropanol/water</td>
<td>100</td>
<td>60 rpm</td>
</tr>
</tbody>
</table>
**In vitro release testing**

Flat vs. suspended rings

**Fig. 3.** Sealed glass flasks for in vitro release testing of drug-releasing vaginal rings. A – ring allowed to rest on bottom of flask containing 100 mL of release medium. B – ring suspended by a nylon thread in glass flask containing 200 mL release medium. The nylon string can be seen in the space between the release medium and the blue screw-top lid.
In vitro release testing
Content

- Vaginal rings
- The human vagina
- Methods for *in vitro* release testing
- *In vitro-in vivo* correlations
- Challenges
In vitro-in vivo correlation

% absorbed in vivo vs % dissolved in vitro
Scarcity of IVIVCs for vaginal rings

- Require validation step based on clinical studies, which are expensive and typically require multiple developed formulations showing different release profiles in multiple media.

- Other drug dosage forms are generally more lucrative than vaginal rings → financial incentive to develop IVIVC (e.g. line extensions).

- Non-compendial methods / poor water solubility / long duration of release / non-biorelevant release media.
IVIVC
Matrix rings

A

Residual drug content, after period of clinical use (mg)

$\rightarrow$

Total dose administered in vivo (mg)

$t_0$ / initial drug loading

B

Time (days)

C

Cumulative in vitro drug release (mg)

$\rightarrow$

Total dose administered in vivo (mg)

D

Cumulative in vitro drug release (mg)

Time (days)

IVIVC
**IVIVC**

Reservoir rings

**E**
Residual drug content, after period of clinical use (mg)

\[ t_1 \rightarrow t_2 \rightarrow t_3 \rightarrow t_4 \]

**F**
Total dose administered *in vivo* (mg)

\[ t_1 \rightarrow t_2 \rightarrow t_3 \rightarrow t_4 \]

**G**
Cumulative *in vitro* drug release (mg)

\[ t_1 \rightarrow t_2 \rightarrow t_3 \rightarrow t_4 \]

**H**
Total dose administered *in vivo* (mg)

\[ t_1 \rightarrow t_2 \rightarrow t_3 \rightarrow t_4 \]

Cumulative *in vitro* drug release (mg)
IVIVC

Other

I

AUC (A_{0-\infty})

Cumulative in vitro drug release (mg)

IVIVC

J

Concentration of drug in plasma, vaginal tissue or vaginal fluid

Daily in vitro drug release (mg)
Content

- Vaginal rings
- The human vagina
- Methods for *in vitro* release testing
- *In vitro-in vivo* correlations
- Challenges
Challenges

- No compendial apparatus or methods
- Considerable variation in *in vitro* release testing methods
- Difficulty in selection of release medium for very poorly water soluble drugs
- Difficulty in developing in vitro release methods to match *in vivo* performance
- Few reports describing accelerated *in vitro* release test methods
Thank you for listening!
Appendix 1
Detailed information on marketed vaginal ring products
<table>
<thead>
<tr>
<th><strong>Indication</strong></th>
<th>contraceptive for breastfeeding women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Material &amp; dimensions</strong></td>
<td>silicone elastomer  &lt;br&gt; 56 mm x 9.0 mm  &lt;br&gt; matrix-type</td>
</tr>
<tr>
<td><strong>Duration of use</strong></td>
<td>3 months continuous use</td>
</tr>
<tr>
<td><strong>API</strong></td>
<td>Name</td>
</tr>
<tr>
<td></td>
<td>Loading</td>
</tr>
<tr>
<td></td>
<td>Release rate</td>
</tr>
<tr>
<td></td>
<td>Serum levels</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>progesterone supplementation in the luteal phase; IVF</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td><strong>Material &amp; dimensions</strong></td>
<td>silicone elastomer, 60 mm x 9.0 mm, matrix-type</td>
</tr>
<tr>
<td><strong>Duration of use</strong></td>
<td>3 months continuous use</td>
</tr>
<tr>
<td><strong>API</strong></td>
<td>![Progesterone molecule]</td>
</tr>
<tr>
<td><strong>Name</strong></td>
<td>progesterone</td>
</tr>
<tr>
<td><strong>Loading</strong></td>
<td>1000 mg</td>
</tr>
<tr>
<td><strong>Release rate</strong></td>
<td>~10 mg/day (in vitro)</td>
</tr>
</tbody>
</table>

Silesia / Pop. Council
1993 (Chile, Ecuador)
**Estring®**

**Pfizer**
1993 (Sweden) / 1996 (USA)

<table>
<thead>
<tr>
<th><strong>Indication</strong></th>
<th>estrogen replacement therapy; local symptoms of menopause</th>
</tr>
</thead>
</table>
| **Material & dimensions** | silicone elastomer (addition cure)  
55 mm x 9.0 mm; 2.0 mm core reservoir-type |
<p>| <strong>Duration of use</strong> | 3 months continuous use |
| <strong>API</strong> |   |
| Name | 17β-estradiol |
| Loading | 2 mg |
| Release rate | 7.5 μg/day |</p>
<table>
<thead>
<tr>
<th><strong>Indication</strong></th>
<th>hormonal contraception (98–99% ovulation inhibition)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Material &amp; dimensions</strong></td>
<td>poly(ethylene-co-vinyl acetate) (EVA) 54 mm x 4.0 mm reservoir-type</td>
</tr>
<tr>
<td><strong>Duration of use</strong></td>
<td>21 days continuous use each month</td>
</tr>
</tbody>
</table>
| **APIs** | Name: etonogestrel  
Loading: 11.7 mg  
Release rate: 120 μg/day  
Name: ethinyl estradiol  
Loading: 2.7 mg  
Release rate: 15 μg/day |
### Indication
hormonal contraception (98–99% ovulation inhibition)

### Material & dimensions
polyurethane sheath and 28% EVA copolymer core / 54 mm x 4.0 mm reservoir-type

### Duration of use
21 days continuous use each month

### APIs

<table>
<thead>
<tr>
<th>Name</th>
<th>Loading</th>
<th>Release rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>etonogestrel</td>
<td>11.0 mg</td>
<td>120 μg/day</td>
</tr>
<tr>
<td>ethinyl estradiol</td>
<td>3.47 mg</td>
<td>15 μg/day</td>
</tr>
</tbody>
</table>
**Femring®**

**Galen / WC / Actavis**  
2001 (UK) / 2003 (USA)

<table>
<thead>
<tr>
<th><strong>Indication</strong></th>
<th>estrogen replacement therapy; local and systemic symptoms of menopause</th>
</tr>
</thead>
</table>
| **Material & dimensions** | silicone elastomer (condensation cure)  
56 mm x 7.6 mm; 2.0 mm core reservoir-type |
| **Duration of use** | 3 months continuous use |
| **API** | 17β-estradiol-3-acetate |
| **Name** | |
| **Loading** | 12.4 / 24.8 mg |
| **Release rate** | 50 / 100 μg/day |
### Indication
- **hormonal contraceptive**

### Material & dimensions
- silicone elastomer (add. & cond. cure)
- 58 mm x 8.4 mm
- reservoir-type (2 cores)

### Duration of use
- 21 days continuous use each month

### API

<table>
<thead>
<tr>
<th>Name</th>
<th>Loading</th>
<th>Release rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>nestorone</td>
<td>103 mg</td>
<td>150 μg/day</td>
</tr>
<tr>
<td>ethinyl estradiol</td>
<td>17.4 mg</td>
<td>15 μg/day</td>
</tr>
</tbody>
</table>
# Dapivirine

<table>
<thead>
<tr>
<th>Name</th>
<th>dapivirine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading</td>
<td>25 mg</td>
</tr>
<tr>
<td>Release rate</td>
<td></td>
</tr>
<tr>
<td><strong>IPW</strong></td>
<td>2600–180 μg/day</td>
</tr>
<tr>
<td><strong>SVF</strong></td>
<td>350–100 μg/day</td>
</tr>
<tr>
<td>Released</td>
<td></td>
</tr>
<tr>
<td><strong>in vivo</strong></td>
<td>~4 mg</td>
</tr>
</tbody>
</table>

# Indication
vaginal microbicide; prevention of sexual transmission of HIV

# Material & Dimensions
- silicone elastomer (addition cure)
- 54 mm x 7.6 mm matrix-type

# Duration of Use
28-day continuous use

![Chemical structure of dapivirine](image)
The human vagina

Histology

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Type of epithelium</th>
</tr>
</thead>
<tbody>
<tr>
<td>vaginal</td>
<td>stratified squamous, nonkeratinized</td>
</tr>
<tr>
<td>ectocervix</td>
<td>stratified squamous, nonkeratinized</td>
</tr>
<tr>
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Appendix 2

Conditions and assumptions for use of the Higuchi equations to model drug release from matrix-type vaginal rings.
In vitro release testing

Higuchi equation / Conditions

1. Drug transport through the ring is rate limiting, whereas drug transport within the vaginal fluid is rapid.
2. The vaginal tissue acts like a “perfect sink”: The drug concentration in this compartment can be considered to be negligible.
3. The initial drug concentration in the ring is much higher than the solubility of the drug in the ring.
4. The drug is finely dispersed within the ointment base.
5. The drug is initially homogeneously distributed throughout the ring.
6. The dissolution of drug particles within the ring is rapid compared to the diffusion of dissolved drug molecules within the ring.
7. The diffusion coefficient of the drug within the ring is constant and does not depend on time or the position within the ring.
8. The ring does not swell or dissolve during drug release.
Appendix 3
Extra slides
**In vitro release testing**

**In vivo**

<table>
<thead>
<tr>
<th>Tissue</th>
<th><strong>In vitro</strong></th>
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