In vitro evaluation of a sirolimus-eluting stent using different release test methods

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**Purpose**

**Drug-eluting stents**
- Dosage form for local drug delivery (extended release) to stenosed portions of the vessel wall

**In vitro release testing**
- No stent-specific method established
- Implementation of flow-conditions and stent embedding in a gel compartment have been shown to impact on in vitro release behavior (1)
- Drug loss may also occur prior to expansion during passage towards site of application

**Concept**
- Estimation of potential drug loss during the passage to the site of implantation using an in vitro model
- In vitro drug release testing from a commercially available drug-eluting stent using different test methods and evaluation whether the used method influences the obtained test results

**Commercial Coroflex® ISAR stent**
- Coated with Sirolimus (SIR, also known as Rapamycin)
- Release controlling agent Protuec (biodegradable)
- Abluminal coating location

**Stent examination**
- Environmental scanning electron microscopy (ESEM)
- Drug elution with MeOH and SIR content determination via HPLC
- Microscopic determination of coating thickness distribution via spectral reflectometry

**In vitro estimation of potential drug losses**
- Model coronary artery pathway adapted from ASTM F-2394-07
- Includes a guiding catheter (a) and a tube (b) perfused with dissolution media, flow-rate 35 mL/min
- Rapid advancement of balloon-mounted stent through perfused system
- Resting at the marked position (*) until completion of perfusion time (5 min including advancement)

**In vitro release testing**
- Use of different test apparatuses: incubation in shaken vial, incubation in stirred beaker, flow-through cell (FTC), reciprocating holder (USP 7), vial-simulating flow-through cell (vFTC) including gelled acceptor compartment and central perfusion through stent lumen
- Dissolution media 0.9 % saline solution containing 0.05 % polyoxyethylene (23) lauryl ether (Brij 35) and 0.0003 % 4,5-di-tert-4-butylhydroxytoluene (BHT)
- Sink conditions in all setups

**Stent examination**
- 147 ± 12 µg drug load on the stent and 154 ± 7 µg on the balloon surface
- Mean coating thickness of abluminal surface 6.1 ± 3.6 µm and 1.3 ± 1.5 µm on luminal side

**Drug loss during simulated passage to site of application**
- Mean drug loss of 9.4 ± 7.9 % during simulated passage incl. 5 min perfusion

**In vitro drug release testing**
- Very different results in dependency of applied test method (range of 61-108 µg released into media within 30 h)
- Fastest release upon incubation in stirred beaker
- Slowest release upon incubation in shaken vial in spite of higher volume and same sampling times as USP 7
- Distinct differences between USP 7 at 5 dpm and 40 dpm

**Conclusion**
- Microscopic examination and drug load distribution indicate coating of the balloon-mounted stent
- Potential drug loss during passage to site of application variable with higher loss during the advancement (abrasion forces) as opposed to the resting time (dissolution)
- In vitro drug release dependent on used test method and most likely also on media (not examined here)
- Difference in release in the USP 7 in dependency of the dip rate in combination with the highest release in the stirred beaker with harsh stirring conditions may indicate a strong influence of hydrodynamics in the test system on the release profile of the tested stent system

**Results**

**Method**

<table>
<thead>
<tr>
<th>Method</th>
<th>Medium condition</th>
<th>Dissolution media</th>
<th>Sink condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>USP 7</td>
<td>45 dpm 10 mL</td>
<td>35 mL/min</td>
<td>no</td>
</tr>
<tr>
<td>USP 7</td>
<td>72 dpm 10 mL</td>
<td>35 mL/min</td>
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</tr>
<tr>
<td>Reciprobat 50</td>
<td>150 mL 100 mL</td>
<td>35 mL/min</td>
<td>no</td>
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<tr>
<td>FTC</td>
<td>35 mL/min</td>
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</tr>
<tr>
<td>vFTC</td>
<td>35 mL/min</td>
<td>35 mL/min</td>
<td>no</td>
</tr>
</tbody>
</table>

**Conclusions**

**References**

**Acknowledgement**

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**In vitro release profiles of drug eluting stents are the dependent on in vitro test method**

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