M 1053

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

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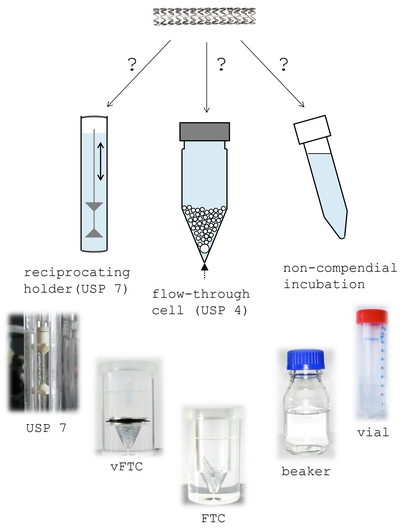
Purpose



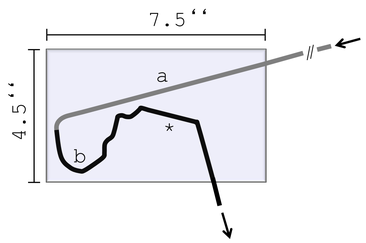
Drug-eluting stents
- Dosage form for local drug delivery (extended release) to stenosed portions of the vessel wall

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 Probucol (bioresorbable)
- Abluminal coating location

Methods



Model coronary artery pathway

Characteristics of in vitro test methods

method	agitation condition	media volume	media exchange
USP 7	40 dpm	10 mL	yes
USP 7	5 dpm	10 mL	yes
vial	shaking incubator	20 mL	yes
beaker	magnetic stir bar	150 mL	no
FTC	perfusion 35 mL/min	150 mL	no
vFTC	perfusion 35 mL/min	150 mL	no

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), vessel-simulating flow-through cell (vFTC)including gelled acceptor compartment and central perfusion through stent lumen
- Dissolution media 0.9 % saline solution containing 0.05 % polyoxyethylen (23) laurylether (Brij 35) and 0.0003 % 3,5-di-tert-4-butylhydroxytoluene (BHT)
- Sink conditions in all setups

Results

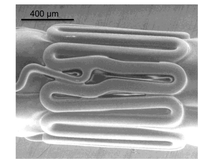
Stent examination
- 147 ± 12 µg drug load on the stent and 154 ± 7 µg on the balloon surface
- Mean coating thickness of abluminal side 6.1 ± 3.6 µm and 1.3 ± 1.5 µm on luminal side

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

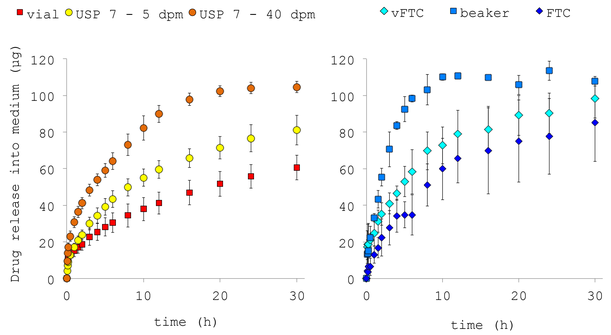
In vitro drug release testing
- Very different results in dependency of applied test method (range of 61-108 µg released into media within 30 h)
- Fastest release upon incubation in stirred beaker
- Slowest release upon incubation in shaken vial in spite of higher volume and same sampling times as USP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

SIR loss during simulated passage to site of application

stent #	SIR loss 1st min (µg)	SIR loss total (µg)	SIR loss total (% of detec. amount)
1	10.4	15.7	5.6
2	28.3	47.8	18.5
3	9.0	11.9	4.1



ESEM image of distal part of crimped stent



SIR release into media over time, n = 3 per method, means ± SD

Conclusion

Conclusions
- 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) 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

In vitro release profiles of drug-eluting stents are highly dependent on the employed in vitro test method

References
[1] Neubert et al., J Control Release 2008; 130 (1): 2-8.

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