Assessment of drug incorporation and release from a novel coronary stent coating

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Introduction

The introduction of drug eluting stents (DES) for the treatment of coronary heart disease has significantly reduced in-stent restenosis, however the use of cytostatic agents causes delayed re-endothelialisation of the target vessel. Here we describe the drug release profiles for rapamycin incorporated into a novel acrylic-based polymer designed to promote vascular re-endothelialisation. 2 Understanding drug release from the surface of DES is integral to the stent development process. It is useful for testing the reliability and reproducibility of coatings and for providing insight into mechanisms of drug release. 1

Experimental Methods

A polymer coating, BTL *Accelerate*™ AT, proprietary to Biomer Technology Ltd, was applied to glass coverslips by dip-coating. Varying AT/rapamycin(R) coating concentration and ATR ratios, see **Table 1**, were assessed for release of drug over a period of 28 days (n=6). Coverslips were immersed in 1.5 ml of release medium, phosphate buffered saline:ethanol (90:10), and were transferred to fresh release medium at regular sampling points, to maintain sink conditions. Initial drug load was determined by immersing coverslips (n=2) in 1.5 ml of methanol every 24 hours for 7 days. The amount of rapamycin in release medium was determined by ultraviolet spectroscopy. Comparisons were drawn between all formulations tested using 2-way ANOVA with Bonferronis post-test. Significance was considered $P<0.05$.

Sample	Bottom Coat	Top Coat	Drug Load (µg)
1	2% AT/R (50:50)	None	32
2	2% AT/R (50:50)	2% AT	19
3	2% AT/R (50:50)	2% AT/R (50:50)	39
4	8% AT/R (80:20)	None	66
5	8% AT/R (80:20)	8% AT	62
6	8% AT/R (80:20)	8% AT/R (80:20)	149

Table 1: Formulations of polymer/rapamycin used to coat glass coverslips used for drug release profile determination. AT=polymer, R=rapamycin.

Results and Discussion

The cumulative amount of drug released over the release period for all formulations is shown in **figure 1** (1 vs 2 $p<0.01$, all others $p<0.001$ at 28 days). The release profiles generated were similar to those for stents used clinically, such as the ENDEAVOR stent which releases the majority of its dose within 2 weeks. 3 Coatings with a high AT/R ratio eluted drug at a significantly slower rate than the low ratio formulations and this was most apparent in the initial 24 hours of the release period (**Figure 2**).This is in line with stents that been used in the clinic such as the TAXUS stent, which was coated with high and low polymer/drug ratios to yield slow and medium rate release profiles, respectively[4]. The cumulative release of initial drug load, **figure 3,** indicates that high AT/R ratio formulations eluted a significantly lower percentage of drug during the initial 24 hours. This is comparable to the Cypher DES which released around 80% of drug load after 30 days.[3] The total amount of drug released over the release period could be controlled by addition of a drug free polymer only top coat combined with a high AT/R bottom coating, which reduced the drug amount released (**figure 3**).

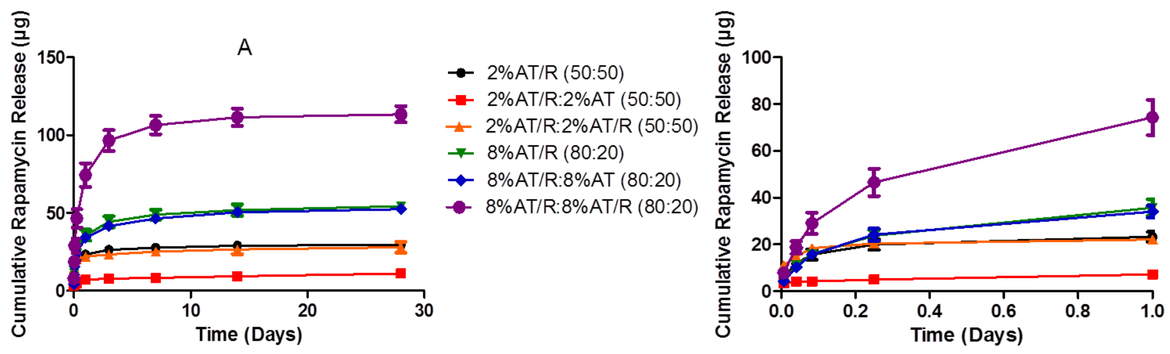

Figure 1: Cumulative release of rapamycin. Right panel: focus on 24 hour period.

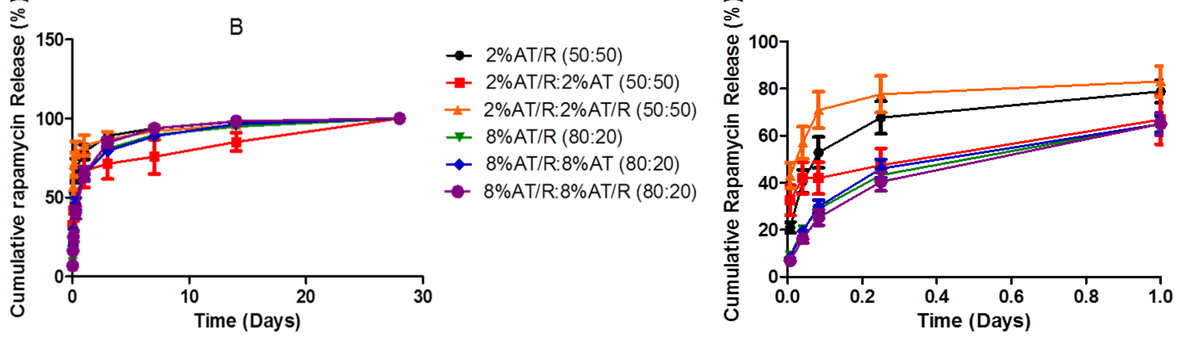

Figure 2: Cumulative percentage release of rapamycin. Right panel: focus on 24 hour period.

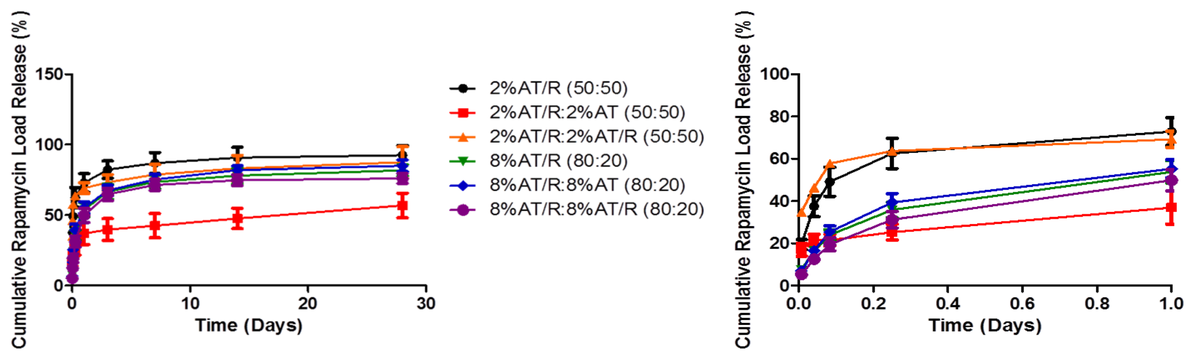

Figure 3: Cumulative percentage release of rapamycin initial load. Right panel: focus on 24 hour period.

Conclusions

This study has demonstrated that rapamycin can be incorporated and released in clinically relevant concentrations, from a polymer designed to promote re-endothelialisation. Future *in vivo* studies will investigate the potential of this polymer/drug coating as an advanced stent coating.

References

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