Bilayer Coated Ureteral Stent as Drug Delivery Platform to Treat Ureteric Diseases

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ABSTRACT

The current methods of treating ureteric diseases such as strictures and carcinoma include endoscopic full-thickness incision of the ureteric wall and placement of an indwelling stent for up to 6 weeks. However, such interventions are not always successful, have high rates of obstruction recurrence, and require repeated interventions. It has been reported that postoperative administration of adjuvant topical drugs can reduce recurrence of ureteric disease. However, the challenge remains to achieve efficacious drug concentration in the target tissue. Current indwelling stents serve only as passive internal scaffolds and do not address any pathology e.g. fibrosis, infection, tumours. The devised technology relates to a drug-eluting ureteric stent that delivers the therapeutic agent into the diseased ureteric tissues via a swellable hydrogel coating. Drug diffusion and transport into the ureteric tissue is enhanced as the hydrogel swells and contacts with the ureteric wall.

Keywords: Hydrogel, ureteral stent, ureteral stricture, upper tract urothelial carcinoma, poly-L-lactide-co-caprolactone

1 BACKGROUND

The ureters in humans are subject to disorders including carcinoma and strictures due to stones or iatrogenic injuries. The primary therapy for benign strictures is endoscopic incision followed by stenting. Stents act as temporary internal scaffolds to allow the ureter wall to heal, and are eventually removed. Despite the high rate of stricture recurrence, no therapeutic options are available for reducing re-stricturing of the ureter. Mitomycin C has been employed as an anti-fibrotic agent used to reduce strictures in some tissues but has not found application in the ureter. In upper tract urothelial carcinomas, the initial treatment involves endoscopic ablation of the tumour followed by stenting. Intravesical instillation of mitomycin C (MMC) is used as adjuvant chemotherapy for bladder cancers, in order to reduce recurrences and disease progression [1]. However in the ureter, the delivery of chemotherapeutic agents in an efficacious manner has been hampered by 1) the lack of a localized delivery option, and 2) the impermeability of the urothelium lining towards drug uptake [2]. Hence, it is desirable that a new mode of therapy involving localized delivery of drug within the ureter be devised for strictures, carcinomas and other ureteric conditions. Localized drug delivery to diseased tissues has also the added benefit of reducing side-effects associated with systemic therapy. It has been reported that increasing the dwell time of the drug during intravesical instillation led to reduced recurrence of bladder tumours [3]. Therefore, it is plausible that increasing the duration of direct contact between the drug and urothelial tissues can lead to an increase in drug uptake and efficacy. As an indwelling stent is routinely placed as an adjunct to surgery for various ureteric conditions, it is ideal to develop a technology around the ureteric stent such that it can be easily integrated into the current treatment workflow for clincians.

2 DEVELOPMENT

Sustained drug release systems and formulations are widely used to improve the efficacy of existing drugs. In the context of ureteric delivery, a localized and sustained delivery could be achieved by utilizing coatings on existing indwelling stents. One challenge facing successful localized delivery is the continuous flow of urine down the ureter. Hence, a delivery platform that enables direct contact between the drug-containing matrix/reservoir and the ureteric tissues also increases drug transfer by minimizing drug washoff by urine. The design and fabrication steps of our delivery platftom are detailed in the following sub-sections.

2.1 Coated Stent Design

The delivery platform comprises of a conventional Double J ureteral stent with a bilayer coating (**Fig. 1**). The first layer comprises of a biodegradable polymer coating dispersed with the drug, and the second layer is a hydrogel which swells sufficiently as it absorbs urine to contact the ureteric wall.

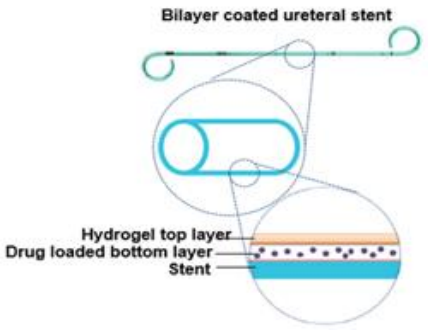

Figure 1. Schematic of ureteral stent coated with drug-eluting polymer and hydrogel layers.

3 IN VITRO CHARACTERIZATION AND RELEASE

The fabricated bilayer coated stent was characterized using scanning electron microscopy, measurement of swelling ratios, and release of MMC in static and dynamic conditions.

3.1 Scanning Electron Microscopy

Under scanning electron microscopy (SEM), the distinct layers of the bilayer coating with uniform thickness were clearly observed in the cross-section of coated stent (**Fig. 2**). These observations exemplified the quality of our coating methodology.

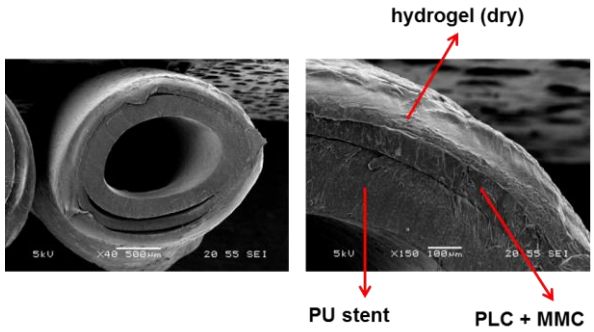

Figure 2. Scanning electron micrographs (SEM) of the coated ureteral stents showing the distinct poly(lactide-co-caprolactone) (PLC)/MMC and hydrogel layers on the polyurethane (PU) stent surface.

3.2 Swelling Ratio and Mechanical Stability

As our platform is dependent on the swelling of the hydrogel to contact the ureter wall, the swelling ratios of different weight % of hydrogels in physiolgical buffer (pH=7.4) were evaluated over 28 days. The hydrogels fabricated by crosslinking 5 wt % solution could swell to 32x its dry mass by the day 2, but experienced mass loss due to degradation and leaching of degraded chains (**Fig. 3**). 7.5 wt % and 10 wt % hydrogels reached 20x and 15x on day 1, respectivly, and largely maintained their wet mass over 21 days in buffer.

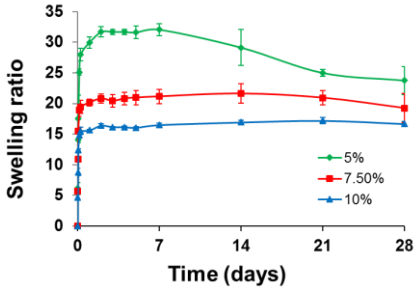

Figure 3. Swelling ratios of 5, 7.5, and 10 wt % hydrogels over 28 days in phosphate buffered saline (PBS), measured by wet mass/original dry mass.

3.3 In Vitro Drug Release in Static Condition

Sustained drug release of the bilayer coated stent was evaluated over the 4-week period with different % loading (**Fig. 3A**) and PLC coating thickness (**Fig. 3B**). Drug release, as a proportion to loaded amount, was the fastest with 2.5 % MMC loading (28% of MMC released by day 28) and slowest in the 7.5 % MMC loading (58% released by day 28), as higher concentrations of drugs require longer solubilization time within the polymer matrix before release. The MMC release rate was observed to be inversely proportional to the polymer thickness due to shorter diffusion path length for thinner coatings. The release profiles for all observations followed first order kinetics, and was not attenuated significantly by the absence of the hydrogel (**Fig. 3C**). Taken together, these release studies in static conditions demonstrated a sustained release of MMC (> 4 weeks) that is tunable by adjusting drug loading and polymer thickness.

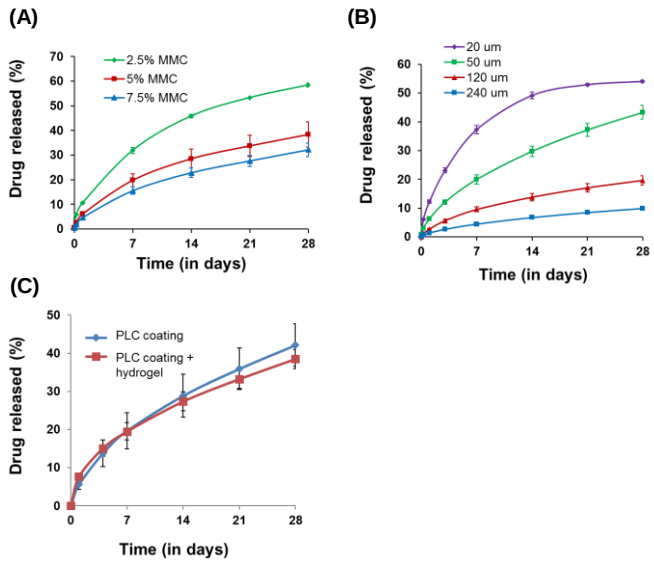

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Figure 3. (A) The cumulative release of MMC from 2.5, 5 and 7.5 wt % drug loaded PLC over 28 days and **(B)** the effect of polymer thickness on the drug release kinetics. **(C)** The release of MMC from a bilyaer coated stent vs PLC-only coated stent.

3.4 In Vitro Drug Release in Dynamic Model

In order to attain drug release data using a more physiological model, a dynamic ureter flow model with a fluid flow rate of 0.5 ml/min at 37 ºC was set up (**Fig. 4**).

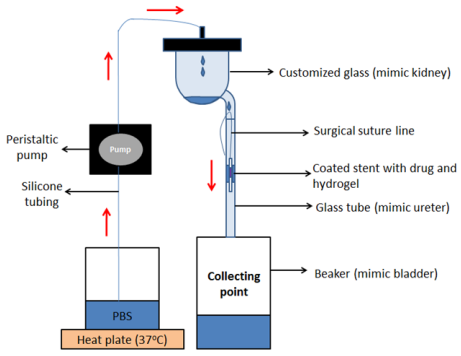

Figure 4. Schematic of the *in vitro* dynamic model for the investigation of MMC release.

The cumulative MMC release of the coated stent was significantly higher with the hydrogel coating than without the hydrogel (**Fig. 5)**. This is attributed to the continuous contact of the PLC coating with the large hydrogel volume, ensuring that concentration gradients drive Fickian diffusion of MMC from the PLC matrix through the hydrogel, and into the outer dissolution volume [4]. In the case of the non-hydrogel coated stent, the PLC matrix is in contact with the dripping fluid intermittently, and a smaller outer dissolution volume results in a slower release rate.

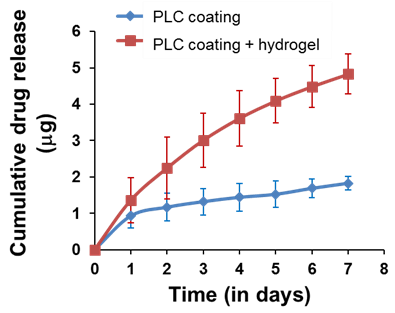

Figure 5. The release of MMC from a bilyaer coated stent vs PLC-only coated stent under dynamic flow condition.

4 IN VIVO FEASIBILITY STUDY IN PORCINE MODEL

To evaluate the feasibility and safety of our delivery platform, we performed a preliminary assesement of the bilayer coated stent in domestic pigs (*Sus scrofa domesticus*). Previous studies suggested that the similarities between human and swine renal anatomy make pigs an appropriate model for urological procedures [5]. The hydrogel coating was imbibed with contrast medium briefly before insertion via cystoscopy. Little resistance was encountered during stent placement, and intravenous urogram (IVU) of the stented ureter on day 3 with administration of radiopaque contrast medium clearly showed that the swollen hydrogel was in contact with the ureter wall (**Fig. 6A**). By using a stent with a larger lumen and minimizing the number of drainage holes the hydrogel covers, we ensured that proper urine flow could occur and hydronephrosis did not develop. There was no difficulty encountered during the removal of the bilayer coated stent via cytoscopy, with the swollen hydrogel coating remaining intact on the stent (**Fig. 6B**).

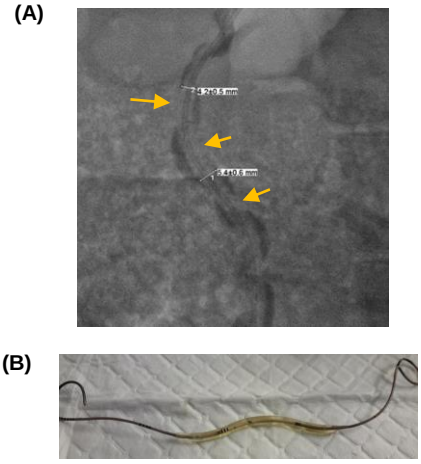

Figure 6. (A) IVU of bilyer coated stent in ureter with flow of contrast medium on day 3 post-stenting. The outline of the stent can be seen clearly, while the contrast-free regions (*arrows*) indicate regions of contact between hydrogel and the ureter walls. **(B)** Explanted stent with swollen hydrogel after removal from the pig ureter using a cystoscope with a grasper.

A short-term assessment of device performance was conducted by measuring tissue drug levels day 1 post-stenting with liquid chromatography mass spectroscopy (LCMS). 384 ng of MMC was found to be transferred into the ureteric tissues. Mean plasma levels were 0.055 ng/mL on day 1 post-stenting. This indicated, for the first time, a successful delivery of a drug from the bilayer coating on the stent to the tissues of the ureteric wall. Further development will center on assessment of tissue drug levels over a longer

period, plasma pharmacokinetics, and histological assessment of the stented ureters.

5 INTELLECTUAL PROPERTY

An international patent application has been filed on the coating technology under PCT: WO2016148648A1 (A stent assembly and method of preparing the stent assembly)

6 CONCLUSION

We have developed a novel bilyer coated indwelling stent for the delivery of chemotherapeutic agents, currently an unmet clinical need for treatment of ureteric conditions such as strictures and upper ureteric cancers. There was sustained release of the model drug, and both safety and proof-of-concept were demonstrated in a porcine model. One value proposition is that ureteral stent placement is a very commonly practiced technique in urology that does not present an additional learning curve to clinicians, and does not alter current treatment workflow. Additionally, the treatment can be easily terminated by stent removal at the clinicians' discretion.

7 ACKNOWLEDGEMENTS

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REFERENCES

[1] KC Latchamsetty and CR Porter, Rev Urol, 8(2): 61–70, 2006.
[2] M Lazzeri, Urol Int, 76(4): 289-295, 2006
[3] EA de Brujin et al, Int J Cancer, 51(3): 359-364, 1992.
[4] TR Hoare and DS Kohane, Polymer, 49 (8): 1993-2007, 2008.
[5] M Swindle et al, Vet Pathol, 49: 344-356, 2012