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# The use of water soluble mucoadhesive gels for the intravesical delivery of epirubicin to the bladder for the treatment of non-muscle invasive bladder cancer.

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Running Title: The development of water soluble gels for the localised delivery of drugs to the bladder

**Keywords**

Epirubicin, Bladder cancer, Intravesical Delivery, HPMC, HEC, Rheology, Gels

**Abstract**

**Objectives:** To develop a epirubicin-loaded water soluble muccoadhesive gels that have the correct rheological properties to facilitate their delivery into the bladder via a catheter, while allowing for their spread across the bladder wall with limited expansion of the bladder and increasing the retention of epirubicin in the bladder and flusing with urine.

**Methods:** Epirubicin-loaded HEC and HPMC gels where manufactured and tested for their rheological properties. Their ability to be pushed through a catheter was also assessed as was their in vitro drug release, spreading in a bladder and retention of epirubicin after flushing with simulated urine.

**Key Findings:** Epirubicin intro drug release was viscosity dependent. The 1 and 1.5% HEC gels and the 1, 1.5 and 2% HPMC gels had the correct viscosity to be administered through a model catheter and spread evenly across the bladder wall under the pressure of the detrusor muscle. The epirubicin-loaded gels had an increased retention time in the bladder when compared to a standard intravesical solution of epirubicin, even after successive flushes with simulated urine.

**Conclusion:** The increased retention of epirubicin in the bladder, by the HEC and HPMC gels warrant further investigation, using an in vivo model, to assess their potential for use as treatment for non-muscle invasive bladder cancer.

## 1 Introduction

Cancer that affects the urinary system (kidneys, ureters, bladder and urethra) is known as urothelial cancer, with the most common type being bladder cancer, which has the highest associated cost of all types of cancer due to the requirements for lifelong treatment and monitoring [1]. 70 to 80% of bladder cancers at diagnosis are non-muscle invasive (NMIBC), 10% of which are classed as carcinoma in situ (CIS), while 70% are at stage Ta and confined to the urothelium with 10% at stage T1 having invaded the lamina propria [2]. Muscle invasive bladder cancers (stages T2, T3 and T4) tend to have spread deeper into the muscle layer, with the propensity to spread to other parts of the body such as the prostate, uterus, pelvis or abdomen.

NMIBC is usually treated by transurethral resection of the bladder tumour (TURBT) followed by an intravesical instillation of either an immune modulator such as BCG or a chemotherapeutic drug, such as mitomycin C or epirubicin, directly into the bladder to reduce the risk of recurrence [3]. Even though TURBT can remove the tumour completely, recurrence occurs between 48 and 70% of the time with progression to muscle invasive bladder cancer occurring between 7 and 40% of the time [4]. Recurrence and progression is dependent on the stage and grade of the tumour, for example the rate of progression in patients with CIS, which is high grade, is greater than 50%, while lower grade Ta tumours rarely progress although they do have a significantly higher recurrence rate [5-6]. A single instillation of chemotherapy immediately after TURBT has shown to significantly reduce recurrence compared with TURBT alone [7]. Intravesical immunotherapy with bacillus Calmette‑Guérin (BCG) is recommended for the

treatment of CIS reducing both the rate of recurrence and disease progression. While BCG immunotherapy after TURBT is recommended to reduce recurrence and disease progression in stage Ta and T1 tumours [8-9]. In patients with high-grade Ta, T1 and CIS lesions a BCG maintenance schedule is recommended, where by BCG maintenance doses are administered every 3 months for the first year and every six months up to 3 years post TURBT [10-13].

The structure of the bladder makes the systemic delivery of drugs very difficult and only a limited amount of drug, delivered systemically, reaches the bladder due to poor absorption and high metabolism rates. Therefore, much higher doses are required, which increases biodistribution and unwanted systemic side-effects [14]. The urothelium layer of the bladder provides a water-tight barrier preventing urine from leaking out of the bladder and into the bloodstream [15] and is comprised of three 3 cell layers [16]: the basal germinal cell layer, the intermediate cell layer and the superficial layer also known as umbrella cells due to their characteristic shape [17]. These umbrella cells are joined by tight junctions, which prevent the passive diffusion of substances across the urothelium layer.

Intravesical drug delivery is the direct administration of drugs to the bladder via a catheter. Because the drugs are administered directly to the bladder the issue of absorption across the urothelium layer is avoided and greatly increases the

exposure of the bladder cancer cells to the chemotherapeutic drug. Furthermore, the reduction in systemic side-effects, due to the limited absorption of drugs across the bladder wall and into the blood stream allows for the delivery of higher doses and more toxic drugs [18-19]. However, intravesical delivery for the treatment of NMIBC has a number of disadvantages such as dilution of the drug with urine, washout of the drug during voiding of the bladder and repeated catheterisation [15]. Studies have shown that using delivery systems with mucoadhesive properties in intravesical drug delivery can significantly increase the retention time of the drug in the bladder [19-20]. Intravesical drug delivery may cause patient discomfort due to expansion of the bladder by the drug solution causing the patient to feel they need to urinate, which may last for up to an hour, causing further stress and anxiety [21]. Furthermore, to ensure that the drug solution is in contact with the bladder wall the patient may need to be rotated, which adds to the discomfort [23].

In this study we demonstrate the potential use of a muccoahesive hydrogel gel based delivery system that will not expand the bladder, but spread evenly along the wall under the pressure of the detrusor muscle, thus alleviating the patients urge to go to the toilet and need to roll the patient, improving patient comfort and acceptance during the treatment session. Furthermore, because these gels are mucoadhesive they increase the retention time of the drug in the bladder, even after simulated bladder voidance.

## 2 Materials and Methods

### *2.1. Materials*

Epirubicin, Hydroxyl Ethyl Cellulose (HEC), Hydroxy Propyl Methyl Cellulose (HPMC), Propyl Ethylene Glycol (PEG), silicone tubing (3mm internal diameter, 4mm external diameter) and sodium dodecyl sulphate (SDS) were purchased from Sigma-Aldrich, (Dorset, UK). Pig bladders where supplied by a local abattoir. All materials were used as supplied.

### *2.2 Preparation of 1% epirubicin-loaded HEC and HPMC gels.*

50mL of 1% Epirubicin-loaded HEC and HMPC gels (1.0, 1.5, 2.0, 2.5 and 3% HEC) were prepared by dispersing the appropriate amount of HEC or HPMC into either 50mL of water which had been heated to 75$^{o}$C or 25mL of water which had been heated to 90oC under continuous stirring. Once the HEC gels began to thicken they were removed from the heat and allowed to cool with continuous stirring. For the HPMC gels the remaining 25mL of water (heated to 50$^{o}$C) was added to the dispersion and once the gels began to thicken they were removed from the heat and allowed to cool with continuous stirring. 5g of epirubicin was dispersed in 12mL of PEG and 1.2mL of this dispersion was added to each of the HEC and HPMC gels and dispersed producing 1% epirubicin-loaded HEC and HPMC gels. The gels were subsequently stored in the fridge until needed.

### *2.3 Determination of the amount of 1% epirubicin-loaded HEC and HPMC gels that can be pushed through a catheter.*

To determine the percentage of gel that can be pushed through a catheter, 10mL of pre-weighed gel was placed into a 20mL syringe, taking care to minimize the entrapment of air. The gel was then pushed through a 43cm long piece of silicone

tubing with an internal diameter of 4mm (which was used to simulate a catheter) into a pre-weighed weight boat and the weight of gel recorded. This weight was then used to calculate the percentage of gel that was pushed through the simulated catheter by dividing it by the initial gel weight and multiplying by 100.

### *2.4 Rheological evaluation of the 1% epirubicin-loaded HEC and HPMC gels*

Continuous flow rheological assessment of the gels was carried out using a TA Instruments AR 2000 rotational Rheometer fitted with a 40 mm diameter steel parallel plate. 1.5g of each gel was placed onto the lower stationary plate of the rheometer using a disposable plastic syringe, and the upper plate was lowered to produce a gap between the plates of 1000 μm. Excess gel was removed before initiating the test. Flow rheology was conducted at 37°C in continuous ramp mode with the shear stress increased from 0 to 450 Pa over 13 minutes (34 sampling points). Viscosity was determined by applying the Power Law on the linear portion of the resulting log-log plot of viscosity against shear rate.

### *2.5 In vitro release of epirubicin from HEC and HPMC gels*

In vitro release of Epirubicin from the HEC and HPMC gels was performed over 24 hours by placing 3 mL of gel (n=4) into a sealed container containing 20mL of Phosphate Buffered Saline (PBS) pH7.4. The containers where then placed into an orbital shaking incubator (Innova 43) at 37$^{o}$C and 60 rpm and the release medium sampled (1mL) with volume replacement at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 4.0, 8.0 and 24.0 hours. Epirubicin concentration of the samples was determined by HPLC analysis.

### 2.6 Spread of epirubicin-loaded and HEC and HPMC gel inside a pig bladder

The spread of the epirubicin-loaded HEC and HPMC gels inside a pig bladder was performed by placing a pig bladder into a pressure chamber and applying 1.8 PSI of pressure to simulate average human detrusor pressure. 10mL of gel was subsequently instilled into the pig bladder using a syringe and silicone tubing 43cm in length with an internal diameter of 3mm and left in place for one hour. The pig bladder was sliced open and the thickness of the gel on 20 different locations of the bladder wall determined.

## 2.7 Determination of epirubicin diffusion across the bladder from both HEC and HPMC gels before and after repeated flushing with simulated urine

A pig bladder was placed into a pressure chamber and a pressure of 1.8 PSI was applied to simulate average human detrusor pressure. 10mL of 1% epirubicin (100mg) gel was subsequently instilled into the pig bladder using a syringe and silicone tubing 43cm in length with an internal diameter of 3mm. The bladder was removed from the pressure chamber and immediately suspended (with the urethra out of solution) in 50mL of PBS pH7.4 solution for 30 minutes when a 1mL sample of PBS was taken and analysed for its epirubicin concentration by HPLC. The bladder was then removed from the PBS solution and flushed with 150mL (the average volume of urine expelled from the bladder upon emptying) of simulated urine and immediately re-suspended in 50mL of fresh PBS for another 30 minutes and another sample taken and analysed. The flushing was repeated a further 3 times and after each flush the concentration of epirubicin in the simulated urine was determined. As a control the above experiment was repeated using 80mg of epirubicin dissolved in 40mL of water which is the current intravesical chemotherapy regimen for treating bladder cancer with epirubicin.

## 2.8 Epirubicin HPLC methodology

HPLC analysis was performed on an Agilent 1200 series HPLC with a Phenomenex Luna C18 4.6 x 150 mm column with a 5μM particle size. The mobile phase was comprised of 50% HPLC grade acetonitrile and 50% phosphate buffer. The flow rate was 1.00mL/min, while UV detection was performed at a wavelength of 233nm with an injection volume of 10μL.

### *2.9 Statistical Analysis*

Statistical analysis was performed using a one way analysis of variance (ANOVA) (GraphPad Prism version 5.02 for Windows, GraphPad Software, San Diego, CA). Post-hoc comparisons of the means were performed using Tukey's Honestly Significance Difference test. A significance level of $p < 0.05$ was accepted to denote significance in all cases.

## 3 Results and Discussion

### *3.1 Determination of the Amount of Gel That can be Pushed Through a Catheter*

When developing a gel based delivery system for intravesical drug delivery you need to ensure that a sufficient volume will pass through the catheter and be delivered to the bladder. In this study we used silicone tubing which had the same length (43cm), internal diameter (4mm) and flexibility as a standard male Foley catheter [22]. The recommended dose of epirubicin in the treatment of bladder cancer is 80mg in 40mL of sterile solution [23]. 10mL of our gel contains 100mg of Epirubicin, thus 80% of our 10mL dose needs to pass through the catheter in order to deliver a dose of 80mg to the bladder. Therefore, we set a limit that 80% of each gel had to pass through the catheter. Figure 1A demonstrates that for the HEC gels at least 80% of the 1 and 1.5% gels can pass through the model catheter, while figure 1B demonstrates that for the HPMC gels at least 80% of the 1, 1.5 and 2% gels can pass through the model catheter. Both figures show a trend of decreasing amount of gel that can be pushed through a catheter with increasing HEC and HPMC loadings. This is to be expected as the higher the loading of either HEC or HPMC the greater the viscosity of the gel.

### *3.2 Rheological Evaluation of the 1% w/w Epirubicin-loaded HEC and HPMC Gels*

The gels where evaluated for their rheological properties and viscosity and the results presented in figure 2. Figure 2A demonstrates that the viscosity of the 2, 2.5 and 3% HEC gels increases at low shear stresses up until and shear stress of between 17 and 30 Pa is achieved, when the gels then demonstrate pseudoplastic shear thinning properties, with the viscosity decreasing as the shear stress is increased. This type of rheological behaviour is undesirable for intravesical drug delivery as the increase in viscosity at low shear stresses is going to make it difficult to push the gel through a

catheter. This is demonstrated in figure 1A where there is a significant drop ($p < 0.05$) in the amount of gel that can be pushed through a catheter between a 1.5 and 2% HEC loading. However, the 1 and 1.5% HEC gels have pseudoplastic shear thinning properties even at low shear stresses (Figure 2A) allowing for more of the gel to pushed through a catheter (Figure 1A). All of the HPMC gels have pseudoplastic shear thinning properties at low shear (Figure 2B), which allows for more of the gels to be pushed through a catheter (Figure 1B) when compared to the HEC gels. However, there is a significant increase in initial viscosity for the 2.5 and 3% HPMC gels (Figure 2B), making it difficult for them to be pushed through a catheter, which is demonstrated in figure1B, with only 55% of the gel being able to be pushed through the catheter.

Figure 2C and 2D demonstrates that there is a linear relationship between viscosity and the HEC and HPMC loadings. As both the HEC and HPMC loadings are increased the viscosity of the gels also increases. This is because HEC and HPMC are well known gelling agents, so the higher the loading or either HEC or HPMC the thicker and more viscous the gel will be. This will have an influence on not only how much of the gel is able to be pushed through a catheter, but also how it spreads on the bladder wall and the release rate of epirubicin from the gel.

### *3.3 In vitro Release of Epirubicin from the HEC and HPMC gels*

The in vitro cumulative release profiles for the epirubicin–loaded HEC and HPMC gels are presented in figures 3A and B respectively. Both figures demonstrate that epirubicin release decreases with an increase in either HEC or HPMC loading, which is due to an increase in the overall viscosity of the gel [24-25]. This is further corroborated by figures 2C and D, which show a linear relationship between the time

taken for each gel to release 30% of its loading and the viscosity of the gel. Furthermore, figures 3C and D also demonstrate that across all the gels, the HEC gels took significantly longer ($p < 0.05$) to release 30% of their total epirubicin loading. This was to be expected as the HEC gels had a significantly higher viscosity ($p < 0.05$) compared to the HPMC gels (Figures 2C and D). The 1% HEC gel released approximately 100% of its epirubicin loading in 24 hours, while the 1.5% HEC gel released approximately 89%. The 2, 2.5 and 3% HEC gels released approximately 56, 48 and 40% of their epirubicin loading over 24 hours respectively. Comparing this to the HPMC gels, where the 1, 1.5 and 2% gels released 100% of their epirubicin content within 24 hours, while the 2.5 and 3% released 90 and 84%, we can clearly see that the HPMC gels have a much faster release rate of epirubicin compared to the HEC gels. One explanation for these findings is that the epirubicin dissolved/dispersed in the gel takes longer to diffuse through the more viscous gels, thus slowing down release [26]. Another contributing factor is the fact that the lower viscosity gels tend to spread out more when they are placed on release exposing more surface area to the release media which would allow for more media to penetrate into the gel while also allowing more epirubicin to diffuse out [26]. This spreading out of the gel would also reduce the distance the epirubicin has to diffuse in order for it to be released. On the other hand the more viscous gels tended to maintain a bolus shape, reducing the surface area of the gel exposed to the release media and increasing the distance the epirubicin has to diffuse.

### *3.4 Spreadability, Retention and Epirubicin Release from both the HEC and HPMC gels Within a pig Bladder*

Based on the amount of gel that could be pushed through a catheter, the rheological behaviour and viscosity of the gels as well as the release rate of epirubicin from the gels we decided to proceed with the 1 and 1.5% HEC gels as well as the 2% HPMC gel. The 2, 2.5 and 3% HEC gels along with the 2.5 and 3% HPMC gel could not be administered through a catheter in sufficient quantities and thus where ruled out. Furthermore, based on their rheological properties it would be difficult for them to spread along the bladder wall under the pressure of the detrusor muscle. The release rate of epirubicin from the 1 and 1.5% HPMC gels was too high and therefore could result in local toxicity in the bladder or systemic absorption, which may lead to unwanted systemic side-effects, while the viscosity of these gels was low and based on their rheological properties they would fail to spread along the bladder wall.

Figure 4A demonstrates that all of the gels spread evenly (small error bars) across the whole of the bladder wall and provided a 0.5mm thick layer (Figure 4B). The gels that where selected had the appropriate viscosity and rheological properties to enable them to spread evenly across the bladder wall. Figure 4C shows that before flushing with simulated urine between 6.1 and 6.5% of epirubicin diffused from the gels and across the bladder wall in 30 minutes, compared to just 3.3% from the control solution. We believe the reason for this is that the control solution is not in contact with all of the bladder wall (hence the need to role/rotate the patient in current intravesical therapy) and thus has a much smaller area of the bladder to diffuse across, whereas the gels coat all of the bladder wall (Figure 4B) with a 0.5mm thick layer of gel, which means there is a much larger area of the bladder wall for the epirubicin to diffuse across. Figure 4C also demonstrates that as the bladder is flushed with urine the

amount of epirubicin which crosses the bladder is significantly ($p < 0.05$) reduced as the epirubicn within the bladder is washed out. This decrease in the amount of epirubicin crossing the bladder wall is much greater for the control solution, which reduced from 3.3% to 0.3% after 1 flush to 0 after two flushes, compared to the gels, where there was still epirubicn crossing the bladder wall after two flushes. This suggests that the gels are better retained in the bladder compared to the solution. This is because the gels are mucoadhesive and stick to the bladder wall [27]. This is further corroborated by figure 4D, which shows the cumulative amount of epirubicin that is flushed out of the bladder. It demonstrates that after the first flush approximately all of the remaining epirubicin in the bladder from the control solution is flushed out, while for the gel solutions approximately 50% is flushed out after one flush, with the remainder flushed out after two or three flushes.

## 4. Conclusion

This paper demonstrates the development of epirubicin-loaded HEC and HPMC mucoadhesive gels, which have the potential to be used in intravesical therapy for the treatment of bladder cancer. The rheological properties and viscosity of these gels allows for their delivery into the bladder via a catheter and in sufficient quantities to have therapeutic efficacy. Furthermore, their rheological properties allow them to spread evenly across the bladder wall under the pressure of the destusor muscle, while limiting the expansion of the bladder. The mucoadhesive properties of the gels increase the retention of epirubicin in the bladder, when compared to the standard intravesical formulation of epirubicin, even after successive flushes with simulated urine. We believe that if successfully tested in an *in vivo* model, these gel formulations offer a more efficient option for the intravesical delivery of chemotherapeutic drugs to the bladder with improved patient acceptability and reduced procedural discomfort or pain.

## Figure Captions

**Figure 1:** The percentage of the various 1% epirubicin-loaded HEC (**A**) and HPMC (**B**) gels that can be pushed through a model catheter.

**Figure 2:** Continuous flow rheograms showing the influence of HEC (**A**) and HPMC (**B**) loading on the viscosity of the 1% epirubicin-loaded gels at increasing shear stress and the effect of HEC (**C**) and HPMC (**D**) loading on the viscosity of the 1% epirubicin-loaded gels.

**Figure 3:** Average (n = 4) *In vitro* cumulative release of epirubicin from both HEC (**A**) and HPMC (**B**) gels into 20mL of PBS pH7.4 and the influence of viscosity on the time for both the HEC (**C**) and HPMC (**D**) gels to release 30% of their epirubicin content.

**Figure 4:** (**A**) The average (n = 20) thickness of gel on the inside wall of a pig bladder. (**B**) A representative image showing the even spread of a gel on the inside of a pig bladder. The percentage of epirubicin that either crossed the bladder wall (**C**) or was flushed out of the bladder (**D**) after successive flushing with simulated urine.

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