British Journal of Pharmacy

https://doi.org/10.5920/bjpharm.1135

British Journal of Pharmacy

www.bjpharm.hud.ac.uk

Proceedings of the 13th APS International PharmSci 2022

Eradication of *E. coli* and *S. aureus* by Ciprofloxacin-loaded hydrogel

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ARTICLE INFO

Received: 16/06/2022
Accepted: 07/07/2022
Published: 04/11/2022

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KEYWORDS: (Ciprofloxacin, biofilms, urinary catheter)

SUMMARY

Hospital-acquired infection is one of the major risks to patients and an economic burden on the healthcare system, and multidrug resistance is a serious complicating factor in providing effective treatment. Novel drug delivery systems for antimicrobial agents can act as a solution for infection. In this study, the authors demonstrate a biomaterial with antimicrobial properties through the incorporation of ciprofloxacin into p(HEMA: MMA) polymer. The main aim is to prevent bacterial adherence on these surfaces, presenting a valuable strategy for nosocomial infection control. The adherence percentage of both S. *aureus* and *E. coli* were significantly decreased, and eradication to the below limit of detection was demonstrated for 24 hr, contributing to decreasing biofilm formation.

INTRODUCTION

Hospital-acquired urinary tract infections (HAUTI) are a common complicating factor of urological practice. This complication related to biofilm formation on the catheter is associated with catheter encrustation for around 50% of all long-term catheterised patients. The general treatment approach is to remove the catheter which is costly (Irwin, McCoy et al. 2013). Complete eradication of medical device-associated infections is difficult due to bacteria being in the biofilm mode of growth. One of the infection control strategies investigated to date is the modification of the biomaterial surfaces by loading the device with an antibacterial agent (McCoy, Irwin et al. 2016). In this study, the authors will examine the release profile of ciprofloxacin-loaded hydrogel at the physiological pH of 7.4 and at the high pH reported at the onset of urinary infection. The microbiological assessments were examined for both gram-positive and gram-negative after 4 hr and 24 hr.

MATERIALS AND METHODS

Ciprofloxacin, 2-hydroxyethyl methacrylate 90% (HEMA), methyl methacrylate 10% (MMA), ethylene glycol dimethacrylate 98% (EDGMA), and benzoyl peroxide 70% (BPO) were obtained from Sigma-Aldrich. Phosphate-buffered saline (PBS), tryptone soya broth (TSB), Mueller-Hinton broth (MHB), and quarter-strength Ringer's solution (QSRS) were obtained from Oxoid Ltd (Hampshire, UK). *S. aureus* ATCC 29213 and *E. coli* ATCC 700928 were used to cultivate in MHB at 37 °C when required for the microbiological assessments. 10 g films of HEMA: MMA (90:10 w/w) were prepared by free radical polymerisation. Post-polymerisation loading was used to load ciprofloxacin into the copolymer. The release profiles of ciprofloxacin were examined in PBS solutions (at pH 7.4 and pH 9) at predetermined time intervals. The antimicrobial action of CIP-loaded p(HEMA-*co*-MMA) copolymers was tested. *S. aureus* and *E. coli* by evaluating the adherence percentage.

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RESULTS AND DISCUSSION

The release profiles of ciprofloxacin from the prepared hydrogel at pH 7.4 and pH 9 are presented in **Figure 1**. The release profile at pH 9 was slightly higher than the lower pH, but with no significant difference in the release between the two different pH solutions.

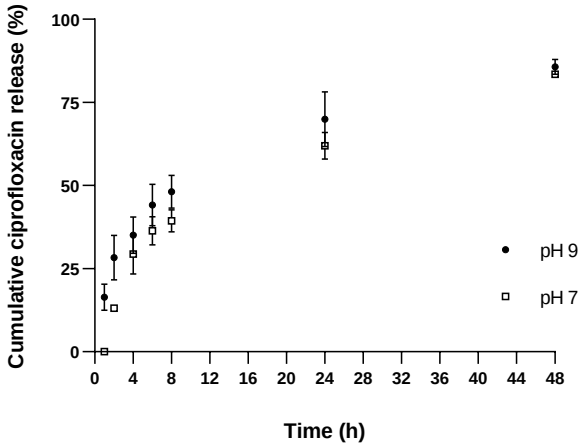

***Fig. 1**. The release profiles of ciprofloxacin at pH 7.4 and pH 9 from the prepared hydrogel p(HEMA: MMA). Error bars represent ± S.D., n = 5.*

As shown in **Figure 2**, less than 60% of ciprofloxacin was released from the hydrogel at pH 7.4 after 24 hours while the release at pH 9 was > 70% after 24 hours. The drug responding to release at two different pH levels and the bioavailability of the drug can be responsive to condition elevated pH such as the onset of urinary catheter infections (Irwin, McCoy et al. 2013). This loading method of the drug on the surface of the model hydrogel suitable to use as a urinary device coating.

Based on the antibacterial efficacy of the hydrogel loaded with ciprofloxacin, the adherence percentage of *E .coli* and *S. aureus* to the surface of polymers loaded with ciprofloxacin were analyzed after 4 h and 24 h incubation (**Figure 2)**.

The results have demonstrated that hydrogel loaded with ciprofloxacin had a significant eradication of gram-positive and gram-negative bacteria for up to 24 hr.

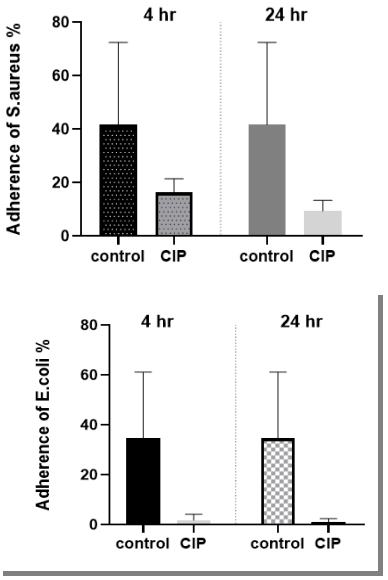

***Fig. 2.** The adherence percentage of E. coli* and *S. aureus on the surface of hydrogel p(HEMA: MMA) (control) and ciprofloxacin-loaded hydrogel p(HEMA:MMA) (CIP) after 4 hr and 24 hr. Error bars represent ± S.D., n = 3.*

CONCLUSIONS

This study describes the rational development of drug loaded hydrogel and microbiological properties of infection-responsive drug delivery system. During urinary catheter infections the pH value of urine is reported to be higher compared with normal physiological urine pH. The findings show that the drug-loaded hydrogel inhibits bacterial growth for at least 24 hours, and significantly improves on the performance of hydrogel not loaded with drug.

ACKNOWLEDGEMENTS

A Scholarship to RM from the University of Jadara, Jordan is gratefully acknowledged.

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