UNIVERSITY OF SÃO PAULO

SCHOOL OF PHARMACEUTICAL SCIENCES OF RIBEIRÃO PRETO

Efeito de carreador lipídico nanoestruturado contendo quitosana em células livres e biofilme de *Escherichia coli*

Effect of nanostructured lipid carrier containing chitosan on free cells and biofilm of *Escherichia coli*

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RESUMO

OSUNGUNNA, M. O. **Efeito de carreador lipídico nanoestruturado contendo quitosana em células livres e biofilme de *Escherichia coli*.** 2019. 73p. Tese (Doutorado). Faculdade de Ciências Farmacêuticas de Ribeirão Preto - Universidade de São Paulo, Ribeirão Preto, 2019.

A infecção do trato urinário (ITU) é a infecção mais comum em nível hospitalar, sendo os cateteres urinários responsáveis por desenvolver o risco de bacteriúria, o que pode agravá-la. Esta infecção geralmente está relacionada a formação de biofilme na superfície interna e externa do cateter. A bactéria uropatogênica *Escherichia coli* continua sendo o microrganismo mais isolado em cateteres e seus biofilmes são estudados de forma a desenvolver estratégias de controle das ITUs. O presente estudo examinou o efeito de um sistema de liberação nanoestruturado contendo quitosana no crescimento de biofilmes uropatogênicos de *E. coli*. Este trabalho foi dividido em duas etapas, sendo a primeira uma comparação de biofilmes crescidos nas superfícies mais utilizadas nos modelos de biofilme in vitro e a segunda a avaliação da suscetibilidade de células livres e biofilme de *E. coli* exposto a um carreador lipídico nanoestruturado contendo quitosana (CLN-quitosana). Assim, biofilmes de *E. coli* foram formados em cateter, lâminas de vidro ou placas de cultura de células por 5 dias, sendo a composição do biofilme avaliada. Na segunda etapa do trabalho, a CLN-quitosana foi preparada usando o método de emulsão e sonicação, sendo caracterizada em relação ao tamanho de partícula, índice de polidispersividade e potencial zeta. Após a determinação das concentrações inibitórias mínimas (CIM) e bactericidas (CBM), os biofilmes de *E. coli* foram crescidos em cateter. Após 48, 72, 96 e 120 horas de crescimento, os biofilmes foram expostos a solução de NaCl a 0,9% (controle negativo), solução de clorexidina a 0,12% (controle positivo) e CLN-quitosana (concentração final de quitosana de 0,28%). Após 24 horas de tratamento, os biofilmes foram coletados para análise de viabilidade bacteriana. Os dados foram analisados estatisticamente pelo teste de Tukey-Kramer ou Tukey, com nível de significância de 5%. A viabilidade bacteriana foi maior no cateter em comparação com lâminas de vidro ou placas de cultura ($p < 0,05$) e a menor contagem bacteriana foi observada na lâmina de vidro ($p < 0,05$). Embora as concentrações de carboidratos tenham sido menores no biofilme formado no cateter ($p < 0,05$), não foram observadas diferenças estatisticamente significativas na quantificação de proteínas para os grupos cateter e placa de cultura ($p > 0,05$) ou entre as lâminas de vidro e a placa ($p > 0,05$). Em relação à segunda etapa do trabalho, a preparação de CLN-quitosana apresentou distribuição bimodal de tamanho de partícula com tamanho médio de 292,9 ± 2,5 nm, índice de polidispersividade de 0,24 ± 0,03 e potencial zeta positivo (+19,1 ± 0,2), indicando o revestimento de nanopartículas pela quitosana. A análise dos valores de CIM e CBM revelou que a formulação inibiu o crescimento bacteriano e exerceu ação bactericida em concentrações 100 vezes maior do que a necessária para o digluconato de clorexidina (controle positivo). Comparado com os grupos controle, a CLN-quitosana afetou a viabilidade bacteriana dos biofilmes em todas as idades avaliadas ($p<0,05$). Sendo assim, os resultados sugerem que o cateter é a superfície adequada para estudar biofilmes de *E. coli*. Tanto as células livres quanto os biofilmes foram afetados pelo CLN-quitosana. No futuro, o cateter urinário pode ser utilizado como modelo para estudar ITUs com populações mistas de bactérias e o efeito de CLN-quitosana ou de sua associação com outros antimicrobianos poderá ser avaliado.

Palavras-chave: Uropatógeno, Biofilme, Cateter, Quitosana, Carreador lipídico nanoestruturado.

ABSTRACT

OSUNGUNNA, M. O. **Effect of nanostructured lipid carrier containing chitosan on free cells and biofilm of *Escherichia coli*.** 2019. 73p. Thesis (Doctorate). Faculty of Pharmaceutical Sciences of Ribeirão Preto – University of São Paulo, Ribeirão Preto, 2019.

Urinary tract infection (UTI) is the most common hospital acquired pathological process and indwelling urinary catheters increase the risk of bacteriuria, which can progress to a serious condition. This infection usually follows formation of biofilm on both the internal and external catheter surface. The uropathogenic bacteria *Escherichia coli* is the most common infecting microorganism on catheter and its biofilms have been studied as a platform to select strategies to control UTIs. The present study examined whether a nano delivery system containing chitosan affected the growth of uropathogenic biofilms of *E. coli*. This work was divided in two stages, the first involved comparing adhesion surfaces most used in in vitro biofilm models and the second evaluated the susceptibility of free cells and biofilm of *E. coli* to a nanostructured lipid carrier coated with chitosan (NLC-chitosan). Thus, *E. coli* biofilms were formed on catheter, glass slides or tissue culture plates for 5 days and the composition of biofilm was evaluated. In the second stage of the work, NLC-chitosan was prepared using the emulsion and sonication method, and further characterized with respect to particle size, polydispersity index, and zeta potential. After determining the minimum inhibitory (MIC) and bactericidal concentrations (MBC), *E. coli* biofilms were grown on catheter specimens. At the 48, 72, 96, and 120 hours of growth, biofilms were exposed to 0.9% NaCl solution (negative control), 0.12% chlorhexidine solution (positive control), or NLC-chitosan (final chitosan concentration of 0.28%). After 24 hours of treatment, the biofilms were collected to analyze their bacterial viability. Data were statistically analyzed by Tukey-Kramer or Tukey test with a level of significance of 5%. Bacterial colony viability was higher in catheter compared to glass slides or plates ($p<0.05$) and the lowest bacterial count was observed for glass slide ($p<0.05$). Although concentrations of carbohydrate were lower in biofilm formed on catheter ($p<0.05$), no differences were observed between catheter and plate ($p>0.05$) as well as glass slides and plate ($p>0.05$) for protein quantification. Regarding second work stage, NLC-chitosan preparation had bimodal particle size distribution with mean size of 292.9 ± 2.5 nm and polydispersity index of 0.24 ± 0.03, and positive zeta potential (+19.1 ± 0.2) indicating the nanoparticle coating by chitosan. Analysis of MIC and MBC values revealed that formulation inhibited bacterial growth and exerted bactericidal action at concentrations 100 times higher than those required for chlorhexidine digluconate (positive control). Compared with the control groups, NLC-chitosan affected bacterial colony viability of biofilms at all ages studied ($p<0.05$). The results suggest that catheter is a proper surface to study *E. coli* biofilm compared to either glass slides or polystyrene plates. In addition, both free cells and biofilms of *E. coli* were significantly affected by NLC-chitosan, which can be a feasible approach for studies using uropathogenic bacteria. In future, urinary catheter can be used as model to study simulated UTIs, using mixed populations of bacteria, and the effect of NLC-chitosan or its association with other antimicrobial agents evaluated.

Keywords: Uropathogen, Biofilm, Catheter, Chitosan, Nanostructured lipid carrier

INTRODUCTION

The use of indwelling medical devices is one of the major causes of urinary tract infections (DOLAN, 2001). The risk of developing a catheter-associated infection increases by approximately 10% each day the catheter is in place (PERCIVAL et al., 2015), and its treatment is challenging because uropathogenic microorganisms adhere to and accumulate on the surfaces of this medical device, producing biofilms (WI; PATEL, 2018).

Biofilms are communities of microorganisms attached to biotic or abiotic surfaces (KUMAR et al., 2017). Several studies have tested catheter as surface to form uropathogenic biofilms but other surfaces such as glass and tissue culture plates also have been used (LEBEAUX et al., 2013). Probably, these surfaces could have significant impacts on biofilm formation and its composition. One of the major features of biofilms is the self-production of extracellular polymeric substances composed of biomolecules such as polysaccharides and proteins that help to protect the microorganisms from external threats, including antimicrobials (KUMAR et al., 2017). In this sense, the development of delivery systems using nanotechnology could be a feasible approach to inhibit biofilm formation or control its growth.

Nanostructured lipid carriers (NLCs) consist of an unstructured solid lipid matrix formed by a mixture of solid and liquid lipids and an aqueous phase containing a surfactant or a mixture of surfactants (BELOQUI et al., 2016), showing advantages such as easy production, low costs and high stability (BUGNICOURT; LADAVIÈRE, 2017). As the unexpected growth of lipid nanoparticles limits their stability, adsorption of chitosan chains to nanoparticles has been used as a promising strategy to improve the formulation stability and bioadhesion (BUGNICOURT; LADAVIÈRE, 2017).

Chitosan is a biodegradable polysaccharide extracted from crustacean shells that is not toxic to animals and humans (MUXIKA et al., 2017). Chitosan and its derivatives have many pharmaceutical applications due to their antimicrobial activity (ALI; AHMED, 2018; CASADIDIO et al., 2019). Considering that the antimicrobial action of “chitosan/lipid” associations on uropathogenic biofilms has not been established in the literature, the present study examined whether cationic NLC covered with chitosan (NLC-chitosan) exert antimicrobial effect against biofilms of *Escherichia coli*, which is one of the most representative bacterial species in catheter-associated urinary tract infection.

CONCLUSIONS

The results suggest that catheter is a proper surface to study *E. coli* biofilm compared to either glass slides or polystyrene plates. In addition, both free cells and biofilms of *E. coli* were significantly affected by NLC-chitosan, which can be a feasible approach for studies using uropathogenic bacteria. In future, urinary catheter can be used as model to study simulated UTIs, using mixed populations of bacteria, and the effect of NLC-chitosan or its association with other antimicrobial agents evaluated.

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