PHARMACOKINETICS OF CLOXACILLIN POLYMERIC NANOPARTICLES ADMINISTERED IN GOATS DIAGNOSED WITH CASEOUS LYMPHADENITIS

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INTRODUCTION

Caseous lymphadenitis (CL), an infectious and zoonotic disease caused by the facultative intracellular bacteria *Corynebacterium pseudotuberculosis*, affects small ruminants worldwide, causing significant reduction in milk, wool and meat production [1]. Considering the current therapeutic approaches, encapsulated lesions on superficial lymph nodes are the most important barrier for penetration of antibiotics into the infection site [2]. Accordingly, the objectives of this study were to evaluate the pharmacokinetics and abscess penetration rate of cloxacillin-loaded polymeric nanospheres (CLXNP) in goats naturally infected with *C. pseudotuberculosis*.

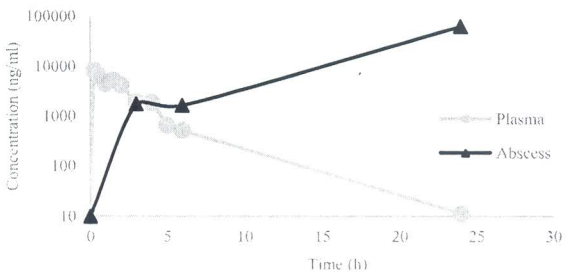
METHODS

CLXNP were produced by PCL interfacial polymerization technique, in accordance with our previous report [3]. CLXNP were characterized by Dynamic Light Scattering (DLS) and Atomic Force Microscopy (AFM) techniques. A total of 08 Toggenburg female goats (Animal Research Ethical Committee protocol nº 011/2014) were distributed into three groups, according to the drainage time of the abscess content: 3, 6 and 24 h after subcutaneous administration of 1.81 mg/kg of CLXNP in the peri-abscess region. Blood was collected at the time 0.25, 0.5, 1.5, 2, 3, 4, 5, 6 and 24 h following drug injection. Intracellular antibacterial activity of CLXNP was determined by in *vitro* infection of macrophages culture by *C. pseudotuberculosis*. Cloxacillin (CLX) quantification was performed by UPLC Tandem Mass Spectrometry.

RESULTS

CLXNP exhibited sizes of 188.41±49.34 nm, polydispersity index (IPD) of 0.181±0.07 and zeta potential of -33.93±6.42 mV. In AFM technique, CLXNP presented spherical shape and a similar size to DLS analysis result. For 4 µg/mL of CLXNP there was a reduction of 96.5 and 89 % in bacterial count at intracellular and extracellular compartment assays, respectively. In plasma, the half-life ($t_{1/2}$) of CLXNP was 3.2 h, maximum concentration (Cmax) was 8312.9 ng/ml, time for peak concentration (Tmax) was 0.3 h, and the area under the curve (AUC_{0-t}) was 22089 ng-hr/ml. For the abscess, the predicted Cmax was 177480 ng/ml, predicted Tmax was 24 h, and AUC_{0-t} was 587886.6 ng-hr/ml.

Graphic 1. Cloxacillin concentration-time curves for plasma and abscess



DISCUSSION & CONCLUSIONS

CLXNP sizes and zeta potential were in accordance with previous reports of our research group [3]. At the in *vitro* assay, the higher rate of bacterial inhibition in the intracellular compartment suggests a delivery of CLXNP to phagocytic cells. Subsequently to single dose administration of CLXNP, considering plasma and abscess CLX concentration patterns, an increasing retention of the antibiotic could be identified in the abscesses during the experiment period. CLX concentration in the abscess was much higher than the in *vitro* inhibitory concentration, even after the antibiotic was no longer detected in the circulatory system. The data are promising for the development of an effective approach for CL treatment.

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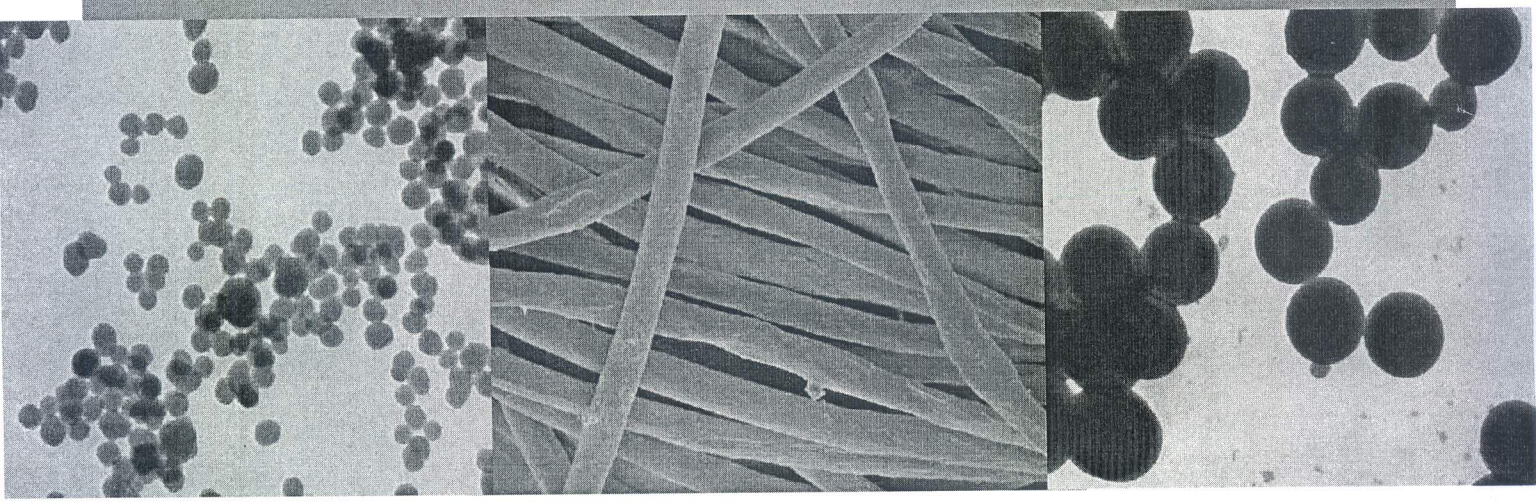

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