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388279 Adsorption and Ion Exchange Processes for Cepharmycin C Purification

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Cepharmycin C (cepC) is a beta-lactam antibiotic produced by the actinomycetes *Streptomyces clavuligerus* and *Nocardia lactamdurans*. It is an important compound for the pharmaceutical industry because it is a raw material for some commercial antibiotics, named as cefoxitin and cefotetan. There are few studies in the literature about purification processes of this antibiotic, and most of the information available is described in patents. It has already been demonstrated that the use of the anionic resin Q Sepharose XL (QXL) in a fixed-bed column was effective in extracting cepC from the broth during column loading. However, the study did not show the separation of any contaminants during elution step, as separated peaks were not observed. Therefore, the method of column operation should be optimized and a deeper study should be carried out.

In this study, three operations in sequence for cepC purification were evaluated, including a different operational method of the fixed-bed column using the resin QXL. The operations consisted of adsorption onto the neutral resin Amberlite XAD4 in a stirred reactor; fixed-bed column process using the resin QXL; and adsorption onto a C18 SPE cartridge. Ultrafiltered broth obtained after fermentation with *S. clavuligerus* was used. Contaminants were monitored during all steps, by different techniques: absorbance measurements between 310 to 400 nm, which are wavelengths that cepC does not absorb; biological assays using *Escherichia coli* ESS, that is a bacteria sensitive to cepC; mass spectrometry analyses.

During adsorption in the stirred reactor with XAD4 resin, 27% of cepC and 44% of contaminants were adsorbed onto the resin. The purification factor obtained was of 1.5. The resulting broth of this step (clarified broth) was used in the fixed-bed column process. Breakthrough curves of the column process showed that cepC and contaminants competed for the binding sites on the resin. Two separated peaks with antibacterial activity were obtained during bed elution, by using 0.1 and 0.5% NaCl solution. CepC was present only in the first fraction. The compounds present in the second peak were not known. Fractions from the center of the peak containing cepC were collected and used in the next step, adsorption in the SPE cartridge. CepC completely adsorbed onto the SPE cartridge, and was eluted using 50% methanol solution. Mass spectrometry analyses of a sample collected in the elution fraction and of the clarified broth showed a reduction in the peaks corresponding to the m/z ratios of contaminants that are difficult to separate, because of the similarity between their molecular structures and that of cepC. The contaminants monitored were penicillin N, deacetylcephalosporin C, deacetoxycephalosporin C and lysine. At this final operation, a partially purified fraction of cepC was obtained. This result is of great relevance since the establishment of a suitable process for cepC purification from fermentation broth has been strongly desired.

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