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Fractionation of Biosynthetic Mixture of Gentamicins by Reactive Extraction

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Abstract : Gentamicin is an aminoglycoside antibiotic industrially obtained by biosynthesis of Micromonospora purpurea or echinospora, the product being a complex mixture of components with very similar structures. Among them, three exhibit the most important biological activity: gentamicins C1, C1a, C2, and C2a. The separation of gentamicin from the fermentation broths at industrial scale is rather difficult and it does not allow the fractionation of the complex mixture of gentamicins in order to increase the therapeutic activity of the product. The aim of our experiments is to analyze the possibility to selectively separate the less active gentamicin, namely gentamicin C1, from the biosynthetic mixture by reactive extraction with di-(2-ethylhexyl) phosphoric acid (D2EHPA) dissolved in dichloromethane, followed selective re-extraction of the most active gentamicins C1a, C2, and C2a. The experiments on the reactive extraction of gentamicins indicated the possibility to separate selectively the gentamicin C1 from the mixture obtained by biosynthesis. The extraction selectivity is positively influenced by increasing the pH-value of an aqueous solution and by using a D2EHPA concentration in organic phase closer to the value needed for an equimolecular ratio between the extractant and this gentamicin. For quantifying the selectivity of separation, the selectivity factor, calculated as the ratio between the degree of reactive extraction of gentamicin C1 and the overall extraction degree of gentamicins were used. The possibility to remove the gentamicin C1 at an extractant concentration of 10 g l-1 and pH = 8 is presented. In these conditions, it was obtained the maximum value of the selectivity factor of 2.14, which corresponds to the modification of the gentamicin C1 concentration from 31.92% in the biosynthetic mixture to 72% in the extract. The re-extraction of gentamicins C1, C1a, C2, and C2a with sulfuric acid from the extract previously obtained by reactive extraction (mixture A – extract obtained by non-selective reactive extraction; mixture B – extract obtained by selective reactive extraction) allows for separating selectively the most active gentamicins C1a, C2, and C2a. For recovering only the active gentamicins C1a, C2, and C2a, the re-extraction must be carried out at very low acid concentrations, far below those corresponding to the stoichiometry of its chemical reactions with these gentamicins. Therefore, the mixture resulted by re-extraction contained 92.6% gentamicins C1a, C2, and C2a. By bringing together the aqueous solutions obtained by reactive extraction and re-extraction, the overall content of the active gentamicins in the final product becomes 89%, their loss reaching 0.3% related to the initial biosynthetic product.

Keywords : di-(2-ethylhexyl) phosphoric acid, gentamicin, reactive extraction, selectivity factor
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