Optimization of asymmetric bio-oxidation with resting cells for preparation of (S)-omeprazole in the chloroform–water biphasic systems using response surface methodology

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Abstract

(S)-Omeprazole is a very effective anti-ulcer medicine, and it is a significant challenge to prepare it by whole cells and to substantially increase the substrate concentration. In the chloroform–water biphasic system, resting cells of the mutant of Rhodococcus rhodochrous(R. rhodochrous)ATCC 4276 were employed to catalyze the bio-oxidation of the omeprazole sulfide for preparation of (S)-omeprazole. At a high substrate concentration(180 mM) and cell concentration(100 g/L), the bio-oxidation was optimized using response surface methodology(RSM), and the optimal yield of (S)-omeprazole obtained was 92.9% with enantiomeric excess(e.e.) (>99%), and no sulfone product was detected under the optimal conditions: the reaction temperature was 37°C, pH of phosphate buffer, 7.3 and the reaction time, 43h respectively. A quadratic polynomial model was established, which predicts the experimental data with very high accuracy according to R2 of 0.9990. The chloroform–water biphasic system may mainly contribute the significant improvement of substrate tolerance because almost all substrates may partitioned in the organic phase (water solubility of omeprazole sulfide is only about 0.5 mg/ml), resulting in little damage and inhibition to cells by substrates. The mutant of R. rhodochrous ATCC 4276 exhibited a high enantioselective, activity and substrate and product tolerance. The aerated flask provides enough oxygen for a high concentration of cells. Accordingly, the bio-oxidation is thus more promising for efficient preparation of chiral sulfoxides.

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