Abstract

An economical and efficient production process of enantioselective synthesis of esomeprazole with an enzyme-catalyzed pyrmetazole oxidation reaction to esomeprazole and crystallization of esomeprazole magnesium dihydrate polimorf with assured assay of R isomer was developed. In the doctoral thesis, we identified the most important factors and parameters that influence the efficiency of the production process of esomeprazole synthesis with the enzyme-catalyzed reaction and the quality of the final product. The amount of reagents, as well as physico-chemical conditions such as oxygen supply and concentration, particle size of the substrate and product, homogeneity of the reaction mixture, foaming prevention, pH value, and configuration of reactors including stirrer, were optimized. The developed process is complex since it involves a combination of chemical and enzymatically catalyzed reactions and various technological approaches to ensure effective mass transfer. It is one of the biggest challenges in the field of industrial biocatalysis, as it involves simultaneous, coordinated action of the three enzymes, the regeneration of the cofactor in the reaction mixture, which is a relatively dense suspension saturated with oxygen, nitrogen and solvent vapor. In the developed process we combined all the necessary attributes and parameters, that enabled us on one hand to provide physical and chemical conditions for the functioning of the enzyme system with intensive mixing, and on the other hand to prevent denaturation of the enzymes as a result of foaming and to successfully complete the transfer into the production process. The critical control parameters were air pressure, mixing conditions, and pH. By optimization of the variables, we achieved at least 96% conversion in less than 24 hours, which is in line with our goals regarding the cost-effectiveness of the process. Critical process parameters were investigated to ensure adequate material quality in the final stage of esomeprazole magnesium dihydrate salt crystallization. Among the qualitative parameters, we focused on the crystallization of the R-isomer and the assuring of the appropriate polymorph. The influence of the other salts impurities, the concentration of the R-isomer and the esomeprasole, the solvent system, mixing and drying on the course and rate of crystallization of the R-isomer and on the quality of the final active ingredient were studied. Using a mathematical model of population balances the crystallization of the R isomer was described.

Keywords: pyrmetazole substrate molecule, enzymatic oxidation reaction, esomeprazole active ingredient, industrial slurry reactor, crystallization downstream process