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INICJATYWA DOSKONAŁOŚCI

ENANCJOSELEKTYWNA BIOTRANSFORMACJA WYBRANYCH SUBSTANCJI CZYNNYCH Z ZASTOSOWANIEM CIECZY JONOWYCH

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SUMMARY

In the 1950s, a drug with the trade name Contergan® containing racemic thalidomide caused tragic adverse reactions in pregnant women.

Due to the different pharmacodynamics and side-effect profile of the individual thalidomide enantiomers, the apparently safe new drug showing analgesic, antiemetic and sedative effects in pregnant women was responsible for significant foetal teratogenicity. The use of the drug by pregnant women resulted in the birth of approximately 12,000 children with the disorder, of which approximately 4 000 did not survive the first year. Because of the dangers of using chiral medicinal products in the form of mixtures of enantiomers or diastereoisomers, for more than 30 years there have been regulations put forward by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) mandating the full characterisation of chiral substances in terms of safety and efficacy for their proposed therapeutic indication. As a result, drug chirality is now an extremely important area in the design and commercialisation phase of new medicinal products, which is particularly evident through the increasing global trend in the number of new enantiomerically pure drugs approved.

One method for obtaining chirally pure substances is kinetic separation based on the use of enzymes acting as enantioselective catalysts. This approach is advantageous from an economic as well as ecological point of view, as biotransformations carried out in this way do not require drastic reaction conditions, which is in line with green chemistry trends. In addition, the use of ionic liquids in enzyme kinetic separations has the additional benefits of reducing the amount of toxic organic solvents used and the possibility of easily separating enzymes from the reaction environment and reusing them in subsequent catalytic cycles.

As part of the completed scientific work, a systematic literature review of scientific studies that addressed kinetic separations of β-blocker drugs was carried out, followed by optimised kinetic separations using biphasic catalytic systems containing ionic liquids for (*R*,*S*)-atenolol, (*R*,*S*)-1-phenylethanol and the carboxylic acid of (*R*,*S*)-clopidogrel.

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The literature review conducted allowed the observation of the benefit of ionic liquids in the kinetic resolutions of β-blocker drugs. Although the studies cited in this paper, carried out by independent research teams, presented different ways of obtaining chirally pure derivatives of β-blocker drugs by enzymatic kinetic separation. However, it was the use of ionic liquids in a two-phase catalytic system that contributed to obtaining products with the highest enantiomeric purity.

In the next stage of the study, the kinetic resolution of (*R*,*S*)-atenolol was optimised using a lipase from *Candida rugosa* in a two-phase catalytic system containing ionic liquids. To this end, a series of studies were carried out to test the effect of different ionic liquids on the performer kinetic resolutions. As a result of these studies, a reaction mixture was proposed to yield chirally pure (*S*)-atenolol acetate.

Subsequently, studies were performed on applying a two-phase reaction system in the kinetic resolution of (*R*,*S*)-1-phenylethanol. The research optimized the enantioselective biotransformation and determined the effect of the acetylating agent, the reaction environment, and the biocatalyst used on the efficiency and enantioselectivity of the kinetic separations performed. As a result, the optimum conditions for enantioselective esterification to obtain chirally pure (*S*)-1-phenylethanol were proposed.

In the final stage of the research work, the kinetic resolution of the carboxylic acid of (*R*,*S*)-clopidogrel was optimised. In the course of the research, the influence of the reaction environments, which differed in organic solvent and ionic liquid, on the enantioselectivity and efficiency of the biotransformations carried out was tested. The completed scientific work made it possible to propose optimum conditions for enantioselective esterification allowing to obtain enantiomerically pure (*S*)-clopidogrel.

Keywords: ionic liquids, biocatalysis, enzymes, lipase, kinetic resolution

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