Diastereomeric salt formationreaction of ibuprofen in supercritical carbon dioxide

Edit Székely[1], David Mendez Sevillano[1], György Bánsághi[1], János Madarász[2], László Vida[1], Béla Simándi[1]

[1]*Department of Chemical and Environmental Process Engineering, Budapest University of Technology and Economics, Budapest, Hungary, H-1111 Budafoki út 8.*

[2]*Department of Inorganic and Analytical Chemistry, Budapest University of Technology and Economics, Budapest, Hungary, H-1111 Gellért tér 4.*

sz-edit@mail.bme.hu

Enantioseparation of ibuprofen was already a topic of several publications, including techniques applying supercritical fluids. However, there were no studies performed the kinetics of diastereomeric salt formation reactions in supercritical carbon dioxide.

The *R*-phenylethylamine forms more stable salt with the *R*-ibuprofen than with the *S*-ibuprofen. The enantioselectivity is also influenced by the applied solvents and crystallisation methods. Supercritical carbon dioxide was applied as reaction media and extraction agent as well. Reactions were performed in a batch reactor unit, after depressurisation of the system and sampling, the unreacted ibuprofen was extracted with carbon dioxide under the same pressure and temperature as the reaction conditions. The results were compared with those when the extraction was performed in a continuous stirred tank reactor (CSTR). Extracts and raffinates were analysed by chiral gas chromatography to determine the enantiomeric ratio and XRD (powder X-ray diffraction) to analyse the crystalline phases. Reaction kinetics, effects of pressure, temperature and reaction time on the achievable resolution efficiency were studied in details in the ranges of 33-80 °C, 10 – 20 MPa and 1 hour – 1 week, respectively. The reaction is not performed under supercritical carbon dioxide if the temperature is as high as 80 °C, due to the very likely inhibition effects on crystal grows of the viscous phenylethylamine – melted ibuprofen liquid phase. At lower temperatures the reaction is fast and enantioselective. At short reaction times the full conversion of phenylethylamine to ibuprofen – phenylethylamine salt was not achieved, furthermore the presence of phenylethylamine-carbonate was detected. Pure ibuprofen- R-phenylethylamine salts were produced in the CSTR with reaction more than six hours. Resolution efficiency (sum of enantoimeric excess values times yields) of 0.39 was achieved at 10 MPa and 39 °C, while with resolution of ibuprofen with atmospheric sample preparation followed by SFE at the same conditions resulted in 0.30 F value.

The research work was supported by Hungarian Scientific Research Fund (OTKA 72861).