

Supercritical antisolvent precipitation for separation of enantiomers

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Effective enantiomeric separation and purity of individual form using environmentally benign solvent is a topic of great interest for pharmaceuticals and food industry due to the different biological activity.[1-4] Hence we studied the diastereomeric salt formation of racemic 2-methoxyphenylacetic acid with enantiopure (*R*)-1- cyclohexylethylamine using gas antisolvent approach in supercritical carbon dioxide. Parametric studies such as effect of different molar ratios, solvents, pressures and temperatures on diastereomeric salt formation reaction were also studied in details.

Reaction procedure involved the dissolution of specific molar ratio of racemates and resolving agent in minimum amount of solvent to form homogeneous phase. These homogeneous phases further allow to react in high pressure autoclave / vessel pressurized with supercritical carbon dioxide. Constant temperature is maintained by using the jacketed thermo bath.

After the reaction, extraction was done with 3 fold volume of supercritical carbon dioxide with respect to reactor volume. Formed reaction products i.e. raffinate and extract were analyzed by chiral gas chromatography.

Wide numbers of polar, non-polar and tuned polarity solvents were screened for the complete solubility of starting materials. Polarity was tuned on mixing of polar and non-polar solvent in certain proportions. Among all combinations acetonitrile and toluene (1:1) mixture was found to be effective.

From the racemic mixture : resolving agent molar ratio study it is revealed that the half equivalent method (2:1) or commonly known as the Pope-Peachy method is suitable for the resolution of racemic MPAA using (*R*)-(-) cyclohexylethylamine (yields and enantiomeric excess values reached 80% and 90%, respectively). Formed diastereomeric salts were characterized using chiral gas chromatography (GC), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR) and X-ray powder diffraction (XRD).

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