INFLUENCE OF PRESSURE ON ANTISOLVENT PRECIPITATION AND PARTICLE SHAPES

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The synthesis and purification of enantiopure compounds using environmentally benign solvent is a topic of great interest for pharmaceuticals due to the different biological activity of the enantiomers. Applying supercritical carbon dioxide as solvent [1] or antisolvent [2-3] opens the route to a process with significantly reduced solvent consumption and often fine-tunable properties of the products by varying the process parameters. This study focuses on the diastereomeric salt formation based resolution of racemic 2-methoxyphenylacetic acid (MPAA) with enantiopure (*R*)-(-)-1-cyclohexylethylamine (CHEA) using gas antisolvent approach with supercritical carbon dioxide (CO_2). The conventional resolution of CHEA with MPAA is known [4], but no study was published on this system and 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 detail. Different crystanality was observed on use of supercritical CO_2 in comparison with classical resolution. Molar ratio study revealed that the half equivalent method or commonly known as the modified Pope-Peachy method is suitable for the resolution of MPAA using (*R*)-(-)-CHEA. Above 50% of enatiomeric excess along with 60% yield was achieved at 120 bar CO_2 and 40°C in 1 hour reaction time.

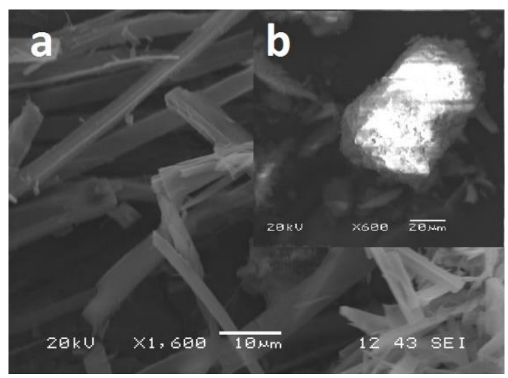

Figure 1: SEM images, for MPAA-CHEA salt formed under pressure (a) and at atmospheric condition (b)

Formed diastereomeric salts were characterized using capillary electrophoresis (CE), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FTIR) and X-ray powder diffraction (XRD). SEM analysis (Fig. 1) clearly shows the different and well defined crystal pattern on use of supercritical CO_2 as antisolvent.

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