523e Resolution of Racemic Mixtures Coupling Crystallization and Simulated Moving Bed: Fundamental Studies for S-Ketamine Production

Georgia O. F. Barros and Everson A. Miranda

The resolution of enantiomers to high levels of enantiomeric purity is presently a requirement in the pharmaceutical industry. However, high purities are reached with this system at the expenses of productivity. Coupling of simulated moving bed (SMB) to a crystallization step can result in a process with a overall higher productivity. The choice of crystallization method for the resolution of racemic mixtures is dependent on the crystal type (conglomerate or racemic compound) and on the location of the eutetic point on the solubility diagram. Eutectic point is the minimum enantiomeric purity that has to be delivered by the SMB to assure that crystallization will produce just one pure isomer. Ketamine is a anesthetic that has a R-isomer with undesirable side-effect. The objective of this work was the development of basic knowledge for a process (identification of the type of racemate and its eutetic point in the solubility diagram) coupling the SMB to a crystalization step in order to produce the S-isomer of ketamine at high enantiomeric purity and productivity. To characterize the crystalline nature of ketamine, X-ray diffraction and infrared spectroscopy of the racemic mixture and pure enantiomers were performed and the solubility curve as a function of temperature was built. The difference between powder X-ray patterns, infrared spectra, and solubility curve slopes of the pure enantiomers and the racemic mixture indicated racemic compound formation. The partial equilibrium phase diagram was constructed and the R:S ratio of the eutectic point was determined (75:25). Batch crystallization assays with initial S:R enantiomeric ratio of 80:20 was carried out at 25ºC in a double walled close glass container (volume 20 or 30 mL), at initial concentration between 150 and 250 g/L. At the present stage of this research, yield and productivity were 71,91% and 6,51 g/(L h). For all conditions, 100% enantiomeric pure S-ketamine crystals were obtained.