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Determination of solubility of paracetamol in supercritical carbon dioxide

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Solubility is a critical parameter influencing all particle formation processes which involve precipitation using supercritical fluids. SEDS, (solution enhanced dispersion by supercritical fluids, York & Hanna 1996) has been developed in our laboratory to achieve a rapid expansion/precipitation process in a highly turbulent flow of solvent modified supercritical carbon dioxide (SF-CO_2). The substance is rapidly dispersed within the fluid as the carrier solvent is simultaneously extracted. The present work is researching analytical techniques to optimise process crystallisation conditions based upon SF-CO_2 solubility behaviour. Temperatures between 40 and 80°C and pressures between 80 and 300 bar were investigated using the model compound paracetamol. Both pure SF-CO_2 or SF-CO_2 modified with ethanol have been investigated.

The equilibrium (static) solubility is measured using a closed system. SF-CO_2 at defined temperature and pressure is continuously passed over a bed of drug substance coated onto glass beads using a magnetic recirculation pump. Samples of the equilibrated mixture are quantified using HPLC. When estimating the SEDS effluent (non-equilibrium) solubility the fluid exiting from the particle formation vessel containing the drug is trapped using cooled ethanol and then analysed off-line by HPLC. The total CO_2 effluent mass is determined using a digital flow meter enabling calculation of the solubility of paracetamol in the effluent SF-CO_2. In addition an extraction method has been devised to analyse the dissolution kinetics of paracetamol. A bed of drug substance coated onto glass beads is packed into a high pressure vessel. The extractant fluid is pumped through the vessel and is then analysed using an on-line HPLC UV detector equipped with a high pressure flow cell. Cooled ethanol is also used to trap the effluent from the detector before it passes through a digital flow meter. The on-line detector response is calibrated using standard solutions of paracetamol in ethanol. This technique was also validated by off-line HPLC analysis of the trap contents, the results agreeing well with the on-line analysis.

By elevating the temperature from 40 to 80°C at 245 bar the equilibrium solubility of paracetamol increased from 5.75×10^{-6} to 1.51×10^{-5} (mole fraction) in pure SF-CO_2. At 40°C and 245 bar, the equilibrium solubility was enhanced to 8.42×10^{-6} in ethanol-modified SF-CO_2 (0.85% mole percent). At 80°C and 245 bar the solubility also increased to 1.71×10^{-5} (mole fraction) in ethanol modified SF-CO_2. These findings were confirmed by the effluent analysis. Furthermore, increasing the velocity of turbulent SF-CO_2 under identical process conditions significantly reduced the residual concentration of paracetamol in the SEDS effluent. At 40°C and 200 bar increasing the solution flow (and hence the level of ethanol modification) also enhanced the residual concentration of paracetamol into the effluent, which is in agreement with the equilibrium solubility data. The extraction analysis correlated well with data obtained from both the equilibrium and effluent analyses and provides a rapid and reliable determination of the solubility behaviour of paracetamol.

References

York, P. and Hanna, M.H., (1996), Proceedings of Respiratory Drug Delivery V, Phoenix, USA, p. 231-239.