Dense Gas Antisolvent Processing of Cyclodextrins from Aqueous Solutions.

N. Foster*[+], R. Mammucari*[+], F. Dehghani*[+]

*Eiffel Technologies Limited
PO Box 1412
Macquarie Centre
North Ryde NSW 2113

[+]School of Chemical Engineering and Industrial Chemistry
The University of New South Wales
Sydney 2052 Australia
N.Foster@unsw.edu.au
Facsimile: +61 (2) 9385 5966

Abstract
In this work the feasibility of processing β-cyclodextrin (β-CD) from aqueous solutions by the Aerosol Solvent Extraction System (ASES) using carbon dioxide modified with ethanol as anti-solvent was studied. The technique is suitable for processing β-CD and water soluble drugs such as amino acids and polypeptides and minimizes residual toxic organic solvent levels in the final product. Submicron particles of β-CD were precipitated at 37°C and 160 bar. The ability to process CD systems from aqueous solutions broadens the application and significance of Dense Gas processing.

Introduction
Complexes between pharmaceutically active compounds (drugs) and cyclodextrins (CDs) are used in the pharmaceutical field for different purposes.[1] In particular, β-CD and its hydrophilic derivatives can be used to improve drug solubility, stability and aerodynamic performance. Cyclodextrins can also reduce side effects and enhance drug permeation in nasal and topical delivery.[1]
The potential of the ASES process for pharmaceutical formulations containing hydrophilic cyclodextrins (CDs) from organic solution has been investigated.[2] Submicron particles of CDs such as ß-CD, methyl-ß-CD (M-ß-CD) and hydroxypropyl-ß-CD (HP-ß-CD) were precipitated from dimethylsulfoxide (DMSO), ethanol and DMSO/ethanol (1/1 volume ratio) solutions using CO_2 as an anti-solvent at pressures between 66 and 80 bar at 25°C. Mixtures of a hydrophobic drug such as naproxen and CDs were dissolved in an organic solvent and co-precipitated by the ASES successfully. Microspheres in the range of 200-500 nm were formed while the dissolution rate of the manufactured product was comparable with the physical mixture prepared by a co-evaporation technique using ammonia at 50°C. The ASES precipitation from organic solutions can be particularly advantageous, when compared to the co-evaporation method, for manufacturing CD systems containing labile components and where control over particle size is important.[2]
The solubility of β-CD in low viscosity organic solvents such as methanol, ethanol, and acetone is limited. However it has high solubility in dimethylsulfoxide (DMSO). The ASES precipitation of β-CD systems from DMSO suffered the drawbacks of the presence of residual

solvent due to the strong intermolecular interaction between DMSO and β-CD. It is proposed that DMSO is included in the β-CD cavity and interacts strongly with the molecule such that it can not be easily removed by washing with CO_2 at the operating conditions examined.[3] In order to eliminate the residual solvent problem, the potential of the ASES technique for manufacturing β-CD from aqueous solutions was examined.

Experimental

The use of ethanol-modified CO_2 as an anti-solvent in the precipitation of CDs from water solutions was investigated. The effects of the nozzle internal diameter (i.d.) and solution flow rate on the characteristics of the product were studied.

Materials

Beta-cyclodextrin was purchased from SIGMA Aldrich. Deionized water (MilliQ) was used as solvent. Ethanol (99.7-100.0% purity, analytical) was purchased from Merck Chemical. Carbon dioxide, (99.9% purity) was purchased from BOC.

Technique

Micronisation of CDs from aqueous solutions was achieved using CO_2 modified with ethanol as anti-solvent. A schematic diagram of the Aerosol Solvent Extraction System (ASES) apparatus is presented in **Figure 1.** A Thermoline Unistat heater circulator controlled the temperature of the system. The pressure of the system was monitored using Druck pressure transducers (model PDCR 911) and Druck pressure indicators. The precipitation vessel included a Jerguson sight gauge series No. 32 with an approximate internal volume of 60 mL and a high-pressure vessel (capacity 150 ml). The presence of the second chamber improved the drying and collection of powder.[4] The insertion of the second chamber, and the absence of the frit from the Jerguson sight gauge, minimized the risk of blockage.

All the experiments were performed at 160 bar and 37°C with ethanol and CO_2 flow rates of 5 and 15 mL/min, respectively. The process was conducted by first pressurizing the precipitation vessel to the desired pressure, and then allowing the DG to flow through the system. Two 500D ISCO pumps were used to run continuously. The ISCO pumps were in the constant pressure mode during each run and the flow rate was adjusted with the valve placed before the vent (V_4 in **Figure 1**). The co-solvent was pumped into the system using an HPLC pump (Agilent 1100 Series). The co-solvent and the CO_2 were mixed on-line using a static mixer (Koflo part No.1/2-.095-3-21H-1TIG) placed in the water bath. The flow rate of each fluid was adjusted to produce a homogeneous mixture with a specific composition. After the system achieved steady state, CD solution was pumped into the precipitation vessel using a Waters M6000A HPLC pump. The solution was sprayed through 20 cm long stainless steel nozzles with different internal diameters (100 or 180 μm). The solution and the modified CO_2 were co-currently delivered into the precipitation vessel. In each run, about 5 mL of aqueous solution were sprayed and the precipitates washed with 270 ml of modified CO_2 at the operating pressure and temperature with a flow rate of 15mL/min. The concentration of ethanol in the CO_2 flow was then gradually reduced to zero. The system was finally flushed with pure CO_2 to remove residual ethanol. The overall washing volume of CO_2 used in each run was 1,600mL.

Particle Morphology

The morphology of the precipitates was analysed by Scanning Electron Microscopy (Hitachi S4500). The samples were put onto aluminum stubs covered with double-sided carbon tape (ProSciTech). Prior to analysis, samples were gold coated with a Polaron Sputter Coater.

Results and Discussion

Beta-cyclodextrin was precipitated from saturated water solutions at 0.3 ml/min aqueous solution flow rate. Discrete microspheres between 100 and 300 nm were produced with an

average recovery of 30%. It was found that at 0.3 ml/min flow rate the characteristics of the powder were not changed when the internal diameter of the nozzle decreased from 180 μm to 100 μm. The particle size of β-CD powder was not significantly changed when the flow rate was decreased from 0.3 ml/min to 0.15 ml/min, however, the recovery was increased at least two fold (60%). A SEM image of the sample is presented in **Figure 2**. The substantial enhancement of recovery may be due to the presence of less water, hence decreasing the CD solubility in CO_2-ethanol-water mixture at operating conditions. Beta-cyclodextrin is not soluble in ethanol and CO_2, but a co-solvency effect of water cannot be excluded. The recovery can be improved by increasing the antisolvent to solvent ratio and extracting the solvent more efficiently. However, the absence of particle aggregation in the product obtained at higher flow rate suggested that solvent extraction was not the critical factor in the precipitation of the CD.

Compared with ASES processing from organic solvent, smaller particles of β-CD were produced and higher recovery was achieved when water was used as a solvent at a similar operating pressure. The ASES precipitation of β-CD from water solutions has the additional advantage of avoiding the use of DMSO which strongly binds to the CD and may contaminate the product.

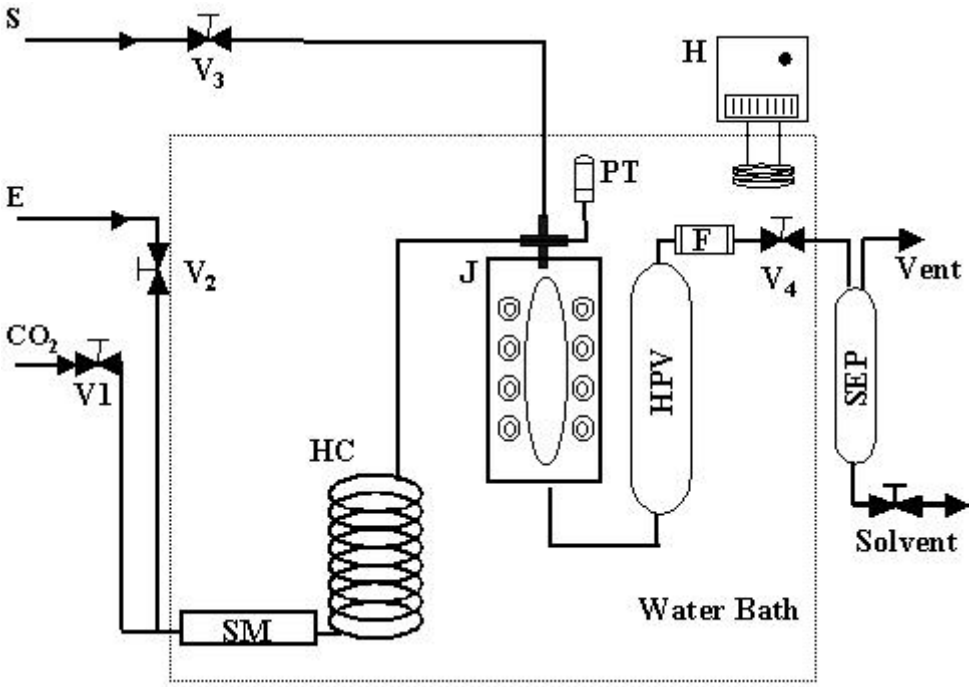

Figure 1. Schematic diagram of the Aerosol Solvent Extraction System (ASES) apparatus. **E** Co-Solvent, **S** Solution, **Vx** Valve, **SM** Static Mixer, **HC** Heating Coil, **J** Jerguson Sight Gauge, **PT** Pressure Transducer and Indicator, **HPV** High Pressure Vessel, **F** Filter, **H** Heater, **SEP** Separator,

Conclusions

In this study the processing of β-CD from water solutions by the ASES technique was studied. The effects of solution concentration, nozzle size and solution flow rate on the product morphology and yield have been considered. Beta-cyclodextrin microspheres were

produced with particles in the range of 100-300 nm and 60% recovery. Particle characteristics were stable upon 3 months storage at room temperature. The yield of the ASES process for manufacturing β–CD from water was higher than precipitation from organic solvent and also achieved smaller particle size. The processing of systems containing β-CD from aqueous solutions can be advantageous, provided that a sufficient amount of the solute can be dissolved, since the use of DMSO can be avoided. Due to the ability of β-CD to increase the aqueous solubility of various hydrophobic compounds, the range of molecules that could be co-precipitated with β-CD from water solutions is presumably broad.Precipitation from aqueous solutions can overcome the drawback of residual organic solvent and allow the co-processing of highly polar active compounds, such as amino acids and polypeptides. The aim of such process could be the improvement of the particulate aerodynamic performance. The process can also be extended to various hydrophobic compounds due to the ability of hydrophilic cyclodextrins to increase the aqueous solubility of a wide range of such compounds.

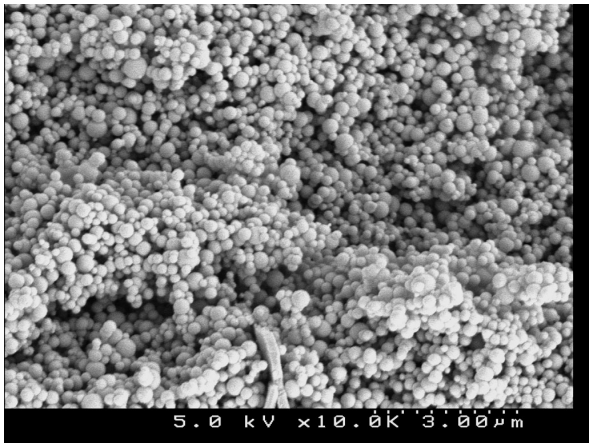

Figure 2. Beta-cyclodextrin particles produced from saturated water solution with a 100 μm nozzle and 0.15 mL/min solution flow rate. The washing stage was performed with neat CO_2.

References

[1] SZEJTLI, J.; OSA, T. Cyclodextrins.; Elsevier Science Ltd., **1996**.
[2] MAMMUCARI, R., DEHGHANI, F., FOSTER, N. R Proceedings of the 8th Meeting on Supercritical Fluids Chemical Reactivity and Material Processing in Supercritical Fluids, Bordeaux, France, April 14-17, **2002** p. 321
[3] BETTING, H.; STOCKHAUSEN, M. Verlag der Zeutschrift fur Naturforschung **1999**, *54*, p. 382
[4] FOSTER, N. R.; REGTOP, H. L.; DEHGHANI, F. WO 2003047553, **2003.**