

Supercritical Fluid Processing of Organic Compounds

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Introduction

Supercritical fluids have sometimes been heralded as enabling revolutionary formulation and synthesis opportunities because of their unique flow and solvent properties. Apart from a well established supercritical fluid extraction industry, the number of applications that has been successfully commercialized to date is somewhat more modest than the degree of research interest would suggest, but there are areas where exciting progress towards commercialization has been made.

A fluid that is above its critical temperature does indeed have distinctive properties. By changing the pressure, the density of the fluid can be varied continuously from a gas-like density to a liquid-like density without a phase change occurring. However, the flow and transport properties of the fluid remain close to that of a gas; thus, it is possible to have both a high solvent capacity (high density) and high gas-like mass transfer and diffusivity rates.

These properties have been used to advantage in the supercritical fluid extraction industry for at least 30 years, for example in de-caffeination of coffee beans and extraction of hops. More recently, there has been interest in using these properties for material formulation and synthesis. The continuously variable solvent properties allow for fractionation of different species, or control of molecular weight in polymerization,¹ by selecting the conditions under which they precipitate from solution. The lack of a phase change, or surface tension, is ideal for uniform and controlled mixing or deposition of layers down to the nanoscale. Moreover, their high transport properties are good for impregnation, rapid supersaturation, and for systems in which reaction rate is limited by mass transfer. By mixing different fluids it is also possible to create solvent systems with a wide range of properties that can be *tuned*, e.g. polarity, hydrogen-bonding behaviour, conductivity, and miscibility or immiscibility with different solvents.²

There is a substantial number of emerging applications in inorganic chemistry, but this article is focused on organic applications, and, more particularly, on organic applications in natural bio-actives, food, and cosmetics, that are of interest to the supercritical fluid processing group at Industrial Research Ltd. (IRL). Applications in these areas tend to limit the useful range of supercritical fluids to those that are non-toxic and have low critical temperatures, e.g. carbon dioxide, light hydrocarbons, and ethers. Many of these fluids are also gases at atmospheric pressure, enabling easy removal of the fluid from products. Alcohols are often used as useful co-solvents, particularly with carbon dioxide, for modifying the polarity.³

Particle Formation Techniques

The physical form of bioactive consumer products, such as pharmaceuticals and nutritional foods, influences many

properties including the bio-availability and stability of the product, as well as ease of storage, handling and consumption. Particle size reduction to sub-micron size is advantageous for improving surface area and bio-availability, particularly for poorly water-soluble compounds, and controlled sizes in the 1-5 μm range are ideal for inhalation dosing of drugs. It is important for many thermally labile compounds to be processed gently and at low temperature to prevent degradation or conformational changes. The low processing temperature of supercritical fluid systems and the low solvent residues that can be obtained give an advantage in some cases over alternative approaches such as milling, spray-drying, and solvent crystallization.⁴

Supercritical fluid processing methods can be categorized according to whether the supercritical fluid is used as a solvent or antisolvent, and whether the supercritical fluid forms a continuous or dispersed phase, as shown in Fig. 1. As a continuous phase solvent, dissolved compounds are precipitated by rapidly decreasing the pressure through a nozzle - the rapid expansion of supercritical solution process (RESS). At the lower pressure the solute is no longer soluble, and the rapid supersaturation and expansion of the fluid enables fine distributed nucleation, and production of a solvent-free product, without high temperatures. This process was described as early as 1984,⁵ and examples of compounds processed include Naproxen, Lovastatin, Cyclosporin A,⁶ and salicylic acid.⁷ Improved dissolution rates are observed, but widespread use of this approach is limited by the low solubility of most compounds in carbon dioxide. Using polar co-solvents or polar supercritical fluids offer viable alternatives, e.g. acetaminophen produced by the RESS process using near-critical dimethyl ether (DME) as the solvent is shown in Fig. 2.⁸ Acetaminophen solubility of up to 15 g/kg in DME is several orders of magnitude higher than in CO_2 .

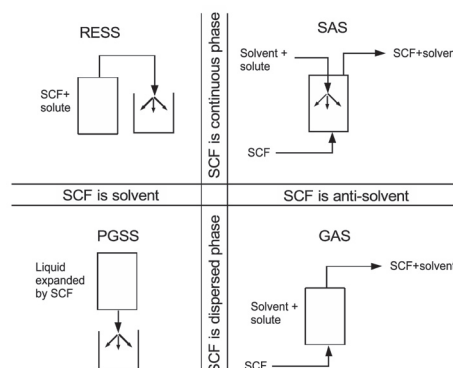


Fig. 1. Schematic of typical contacting arrangements for supercritical fluid (SCF) particle formation and coating

The PGSS process (particles from gas saturated solution - see Fig. 1) works by dissolving the supercritical fluid into the product to reduce the viscosity and, in some cases, the melting point. The *gas-saturated* liquid is then expanded, releasing the dissolved gas, causing atomization and

Joule-Thompson cooling that helps to solidify the product. This process has a much higher throughput than the more dilute RESS process, making it more economically viable, and giving it a wider range of useful applications, particularly with polymeric materials. However, the process is limited to liquid or liquefiable feed materials.

Because of the low solubility of many compounds in CO_2 , it is an effective antisolvent for many systems, as in the SAS (supercritical anti-solvent), and GAS (gas anti-solvent) processes (see Fig. 1). In the SAS process, a solution is contacted with the supercritical fluid where the solvent is highly soluble in the supercritical fluid but the solute is not. The solvent expands into the supercritical fluid until the solute is no longer soluble and a solid precipitate forms. The key advantages are the low temperatures used, the rapid mass transfer and fine particle nucleation that occurs, the improved range of compounds that can be processed compared to the RESS process, and the higher solubilities that can be achieved by choosing an appropriate solvent. Many compounds, including insulin, hydrocortisone, lysozyme, albumin,⁴ and plant and dairy products,⁹⁻¹¹ have been processed. Fig. 3 shows an example of particles of K_2CO_3 formed by this process, by precipitation (and reaction) of KOH with CO_2 from solution in EtOH. In the GAS process, the solution forms the continuous phase and the supercritical antisolvent is introduced, gradually decreasing the solvent capacity of the solution until particles precipitate. Further washing with the supercritical fluid can remove the majority of the solvent from the system. This has been used for many systems, including proteins, but it is a batch process with more limited control over the particle size.

The major disadvantage of the antisolvent process is the presence of residual solvent in the product. Suitable solvents for use with CO_2 include alcohols, but solvents that are less desirable because of their toxicity, such as CH_2Cl_2 and Me_2SO (DMSO), have often been used. Use of other supercritical fluids is possible, including C_2H_6 and NH_3 ,⁴ and DME can be used to precipitate compounds directly from aqueous solution,¹¹ as shown in Fig. 4 for particles of bovine serum albumin produced by the SAS process.

Variations of these types of process can be employed to form more complex systems, including the use of emulsions and sonication to aid phase dispersion. Surfactants and stabilizers can be added to limit re-agglomeration or deterioration of particles that are formed. More extensive reviews of all of these particle formation processes and their applications have been published elsewhere.^{2,4,12-15}

Particle Coating/Composites

Considerable research has been carried out using supercritical fluids for particle coating applications. In organic systems this is largely driven by applications in drug delivery, where the aim is to develop a stable highly bio-available product with a controlled release rate, or to incorporate the drug within compounds that enable targeted delivery.¹² Applications in food, cosmetics, and agricultural products also exist.¹⁶ Expected benefits of supercritical processing technologies over conventional methods include improved particle size and coating control, low

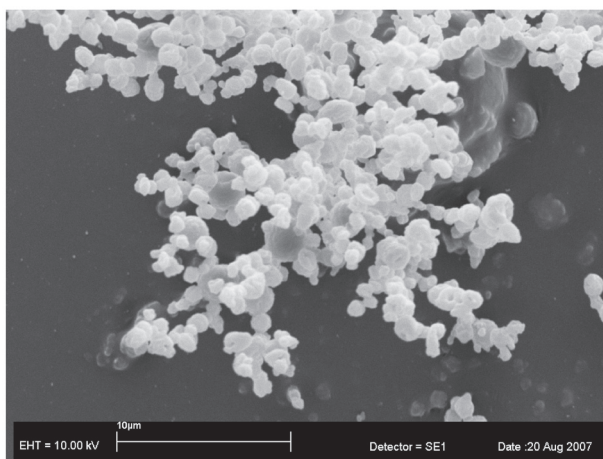


Fig. 2. Acetaminophen particles formed by the RESS process from solution in near-critical dimethyl ether

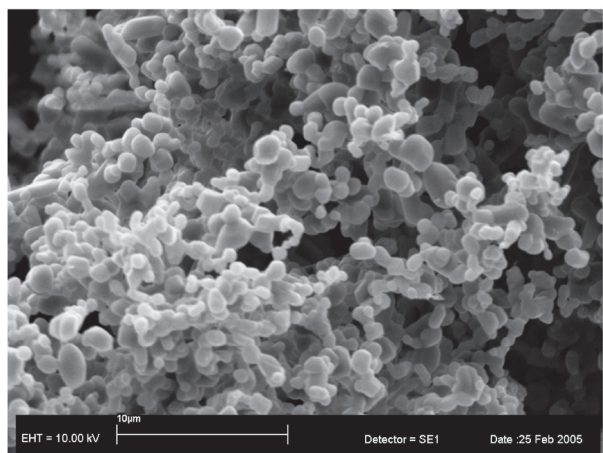


Fig. 3. K_2CO_3 formed by SAS precipitation of KOH from solution in ethanol into supercritical CO_2

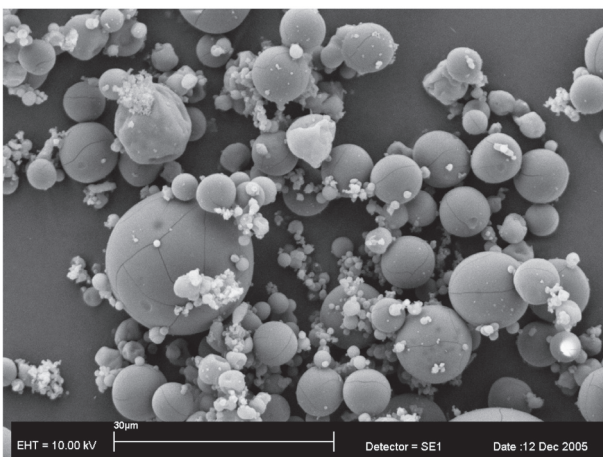


Fig. 4. Bovine serum albumin particles from aqueous solution using DME as antisolvent

temperature processing, and the elimination or reduction in organic solvent use. Composite materials can be formed by surface coating, encapsulation, impregnation, or blending.

If the coating material is soluble in the supercritical fluid, then a RESS- or PGSS-type process can be used. Polymers that are suited to processing using CO_2 include siloxanes, fluoropolymers, and biopolymers such as polylactic acid (PLA) and polyglycolic acid. Polypropylene, polystyrene,

and polymethylmethacrylate have been processed using pentane and propane as the supercritical fluid.¹³ Examples of studies include PLA/lovastatin and PLA/naproxen systems where both the drug and polymer are co-precipitated, although control over the distribution of the components can be difficult using this process. Drugs like nifedipine and felodipine that are liquefied by CO₂ have been coated with polyethyleneglycol by a PGSS process. Polymer coating can also be achieved by expanding polymers that are dissolved, or plasticized, by the supercritical fluid with a suspension of pre-formed drug particulates. Lipid coatings, generally soluble in CO₂, have also been used. Impregnation of polymers or other porous substrates is effective using a supercritical solvent to diffuse compounds into the matrix, e.g. ibuprofen into α -lactose, or β -cyclodextrin,¹⁷ or angiogenic growth factors into poly(lactide-co-glycolide). The use of DME as the supercritical solvent has been described by Perrut *et al.*¹⁵ for formation of drug/polymer composites.

A greater number of processing options are available using supercritical fluids as an antisolvent. Poorly soluble compounds and polar molecules can be processed with a wide range of coatings including polymers, cyclodextrins, lactose and chitosan, as well as inorganics such as magnetite¹⁸ for use in magnetic field directed drug delivery. Compounds, including insulin and DNA have been successfully encapsulated and stabilized using these methods.⁶ CO₂ antisolvent systems are generally used with DMSO or CH₂Cl₂ solvents, and residues of these solvents in the product detract from the other benefits of supercritical fluid processing. Limited work with other supercritical fluid antisolvents has been carried out.^{10,16,19}

Developing New Supercritical Fluid Technologies

Research carried out at IRL, has shown that DME can be used as an effective antisolvent for proteins in aqueous solution, and for water soluble coating compounds. This solvent is non-toxic and there are currently applications in process for registration of it with regulatory bodies in the EU and NZ for use with food products. The high vapour pressure of DME results in negligible residues – levels that we have been unable to detect in typical organic substrates with a measurement resolution of better than 1 ppm. In composite particles produced by co-precipitation of an Amano Lipase enzyme with β -cyclodextrin (Fig. 5), the enzymatic activity was retained, and no DME residue was recorded in the product.

The flammability of DME may have contributed to the limited range of research and development carried out because of the dedicated research facilities required. However, at an industrial level, processing standards for flammable solvents are well established and there are no practical barriers to their commercial use. In aqueous-based processing, or using combinations of inert fluids such as CO₂ with the flammable solvent, the flammability is suppressed.

An important factor in the selection and design of supercritical fluid processing systems is developing an under-

standing of their solvent properties and phase behaviour. Research at IRL and elsewhere enables characterization of supercritical fluid solvent systems. Phase behaviour can be studied either in variable volume pressure cells to measure saturation and dew points, or by sampling phases held in equilibrium and determining their composition.²⁰ Solid solubilities can often be modelled with simple correlations.²¹ Liquid and gas phase separations can be correlated reliably using equation of state models,^{22,23} but they have limited applicability for highly polar compounds, longer chain molecules, or highly complexing systems. More involved interaction models, or the use of molecular dynamics modeling has been applied in these cases with some success. Our recently measures phase boundaries for the dimethyl ether/water system are shown in Fig. 6 at 323 K. Modelling using the Peng Robinson equation of state²³ with corrections described by Wong and Sandler,²⁴ fits both the liquid and vapour phase boundaries well. The presence of a small liquid-liquid-vapour region is also reliably predicted.

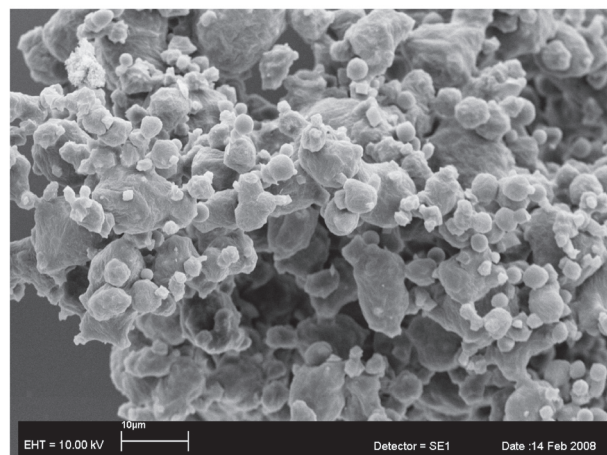


Fig. 5. Composite β -cyclodextrin and Amano Lipase precipitated from aqueous solution using DME as an antisolvent; enzyme activity maintained at >90% of preprocessing levels; DME residues not detected (<1 ppm)

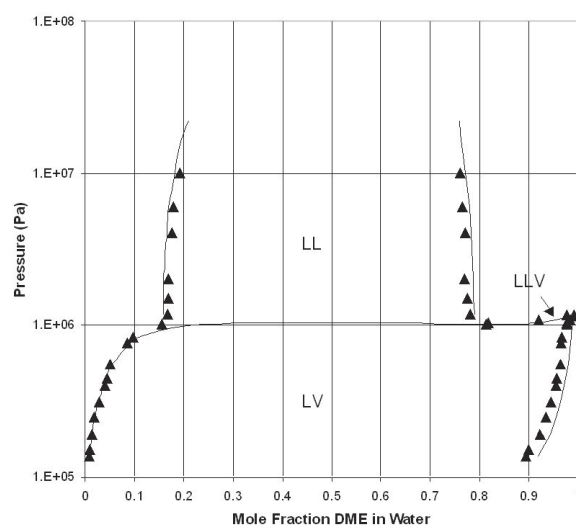


Fig. 6. Phase boundaries for DME and water at 323 K.; solid line: curve fit using the Peng-Robinson equation of state with mixing rules according to Wong and Sandler

Other solvent properties, including di-electric properties, can be measured²⁵ and Fig. 7 shows the variation in permittivity of CO₂ and DME mixtures with pressure and composition. A range of properties from non-polar to the polarity of pure DME can be obtained by varying pressure, temperature, or composition.

It is also important to be able to demonstrate that new processing technologies can be scaled reliably,²⁶ and tested for commercial viability. IRL has developed a range of scales of operation, including pilot scale equipment that can be used to generate commercial samples and engineering design and costing information. A portable pilot scale plant (Fig. 8) is also available for lease, enabling production of test products in regulated food or pharmaceutical facilities.

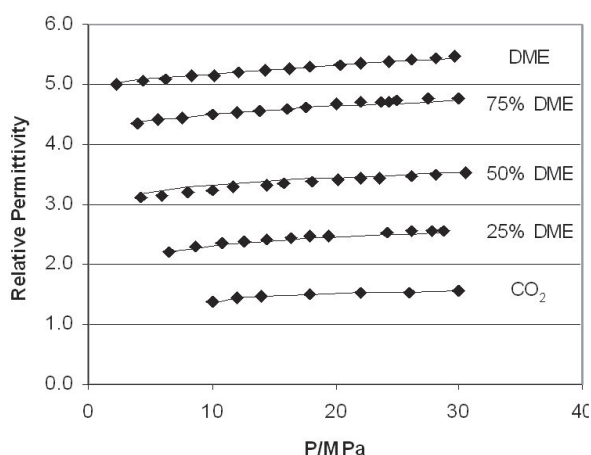


Fig. 7. Relative permittivity of carbon dioxide and dimethyl ether (DME) mixtures at 313 K



Fig. 8. Portable pilot scale supercritical fluid processing plant

References

- Cooper, A. I. *J. Mater. Chem.* **2000**, *10*, 207-234.
- Jessop, P. G.; Subramaniam, B. *Chem. Rev.* **2007**, *107*, 2666-2694.
- Schmitt, W. J.; Reid, R. C. *Fluid Phase Equilib.* **1986**, *32*, 77-99.
- Shoyele, S. A.; Cawthorne, S. *Adv. Drug Del. Rev.* **2008**, *58*, 1009-1029.
- Krukonic, V. *Proc. AIChE Ann. Meeting*, San Francisco, 26-30 Nov 1984, 140F, T-214.
- Tandya, A.; Mammucari, R.; Dehghani, F.; Foster, N. R. *Int. J. Pharmaceut.* **2007**, *328*, 1-11.
- Turk, M.; Lietzow, R. *J. Supercrit. Fluids* **2008**, *45*, 346-355.
- Calderone, M.; Tallon, S.; Fenton, K. *J. Supercrit. Fluids* **2008**, *45*, 245-252.
- Catchpole, O. J.; Tallon, S. J.; Grey, J. B.; Fletcher, K.; Fletcher, A. J. *J. Supercrit. Fluids* **2008**, *45*, 314-321.
- Catchpole, O. J.; Tallon, S. J. Pat. WO/2007/123424, 11/01/2007.
- Tallon, S. J.; Catchpole, O. J.; Fenton, K.; Learmonth, A. *Proc. AIChE Ann. Meeting*, Cincinnati, 30 Oct-4 Nov 2005.
- Ginty, P. J.; Whitaker, M. J.; Shakesheff, K. M.; Howdle, S. M. *Materials Today* **2005**, *8(8) Suppl. 1*, 42-48 (doi:10.1016/S1369-7121(05)71036-1).
- Yeo, S.-D.; Kiran, E. *J. Supercrit. Fluids* **2005**, *34*, 287-308; Jung, J.; Perrut, M. *J. Supercrit. Fluids* **2001**, *20*, 179.
- Fages, J.; Lochard, H.; Letourneau, J. J.; Saucéau, M.; Rodier, E. *Powder Tech.* **2004**, *141*, 219.
- Perrut, M.; Jung, J.; Leboeuf, F. *Int. J. Pharmaceut.* **2005**, *288*, 3-10, 11-16.
- Taki, S.; Badens, E.; Charbit, G. *J. Supercrit. Fluids* **2001**, *21*, 61-70.
- Cristini, F.; Delalonde, M.; Jousset-Dubien, C.; Bataille, B. *Proc. 6th Int. Symp. Supercritical Fluids*, Versailles, France, 28-30 April 2004, 1917-1922.
- Chattopadhyay, P.; Gupta, R. B. *Ind. Eng. Chem. Res.* **2002**, *41*, 6049-6058.
- Bausch, A.; Peter, S. K. F.; Steiner, K.; Stoller, H.; Weidner, E. Pat. WO 9816204, 1998.
- Tallon, S. J.; Catchpole, O. J. *Proc. AIChE Annual Meeting*, Austin, Texas, 7-12 Nov 2004; Catchpole, O. J.; Tallon, S. J.; Dyer, P. J.; Lan, J.-S., et al. *Fluid Phase Equil.* **2005**, *237*, 212-218; Durling, N. E.; Catchpole, O. J.; Tallon, S. J.; Grey, J. B. *Fluid Phase Equil.* **2007**, *252*, 103-113.
- Chrastil, J. *J. Phys. Chem.* **1982**, *86*, 3016-3021.
- Poling, B. E.; Prausnitz, J. M.; O'Connell, J. P. *The properties of gases and liquids*, 5th edn. McGraw-Hill: New York, 2000.
- Peng, D. Y.; Robinson, D. B. *Ind. Eng. Chem. Res.* **1976**, *15*, 59-64.
- Wong, D. S. H.; Sandler, S. I. *Ind. Eng. Chem. Fund.* **1984**, *23*, 348-354.
- Eltringham, W.; Tallon, S. J.; Catchpole, O. J.; Fenton, K. *J. Chem. Eng. Data* **2008**, *53*, 826-829; Eltringham, W.; Catchpole, O. J. *J. Chem. Eng. Data* **2007**, *52*, 363-367.
- Perrut, M.; Clavier, J. Y. *Ind. Eng. Chem. Res.* **2003**, *42*, 6375-6383

