Assessing Feasibility of Supercritical Reaction Processes Using Laboratory Equipment

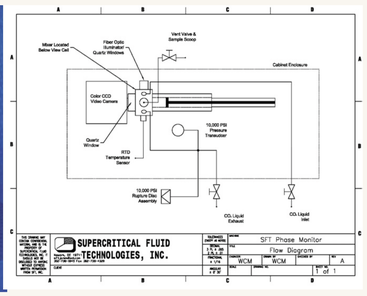
Kenneth J. James, Ph.D., Supercritical Fluid Technologies, Inc., Kenneth R. Krewson, Supercritical Fluid Technologies, Inc*

Abstract

The primary goal of laboratory supercritical fluid reaction unittesting is to assess technical feasibility of a potential supercritical fluid reaction application. Initial screening with a Phase Equilibrium analyzer should be carried out to determine the processing conditions in which the reagents and products of interest solubilizeand/or precipitate from the supercritical fluid. Experimentation thenmoves to the use of a supercritical fluid reaction laboratory unit. The laboratory unit typically has a 50ml to 4 liter reaction vessel fitted with the appropriate reagent addition modules, mixing, flow meters, and sensors. Product samples and data from the feasibility testing are used to assess product quality, and to research process variables such as: 1) Preparation and solubility of reagents 2) Reaction conditions (temperatures, pressures, use of Co-Solvents to enhance reagent or product solubility. 3) Collectionconditions. The reaction product is analyzed to determine how changes in these parameterschange yield, purity, and economics of the proposed process. This information can thenbe utilized to fine tune the reaction to maximize key parameters for a commercial scale supercritical fluid reaction process. Examples demonstrating the use of both and laboratory SFR unit and supercritical fluid phase equilibrium instrument will be presented.

Solubility Experiments –Phase Monitor

Direct, visual observation of materials under supercritical conditions is an important first step in the development and refinement of supercritical fluid reaction process. A specially designed phase equilibrium view cell or "Phase Monitor"is used to observe the dissolution, melting, precipitation, swelling and crystallization of compounds at a wide range of pressures and temperatures. Observations of materials are performed in the supercritical region, under precisely controlled conditions. ThePhase Monitor simplifies the determination of critical point for binary, tertiary or complex mixtures. Through a better understanding of phase behavior as a function of temperature, pressure, co-solvent, and sample concentration, a significant time and cost savings for supercritical process development is realized.Variable-Volume Equilibrium View Cell DesignMain components include a Variable-Volume Equilibrium View Cell, Pressure Generator, Light Source and Color CCD Video Camera, sample mixing, and optional Video Monitor Display Panel Module, PC Video Capture Software, and Co-Solvent Addition Module. Experiments can be Performed from a Few Hundred psi to 10,000 psi (689 Bar, 69 mPa) and from Ambient Temperature to 150odegrees Celsius.



ValidationThe accuracy of the experimental method was validated by comparing the experimentally determined critical point for pure CO_2 with the literature values. The gradual phase transition of carbon dioxide from a single phase supercritical state through the critical point toa two phase subcritical state is pictured below. (The view cell shown here has a glass tube inserted in the cell).


Supercritical state

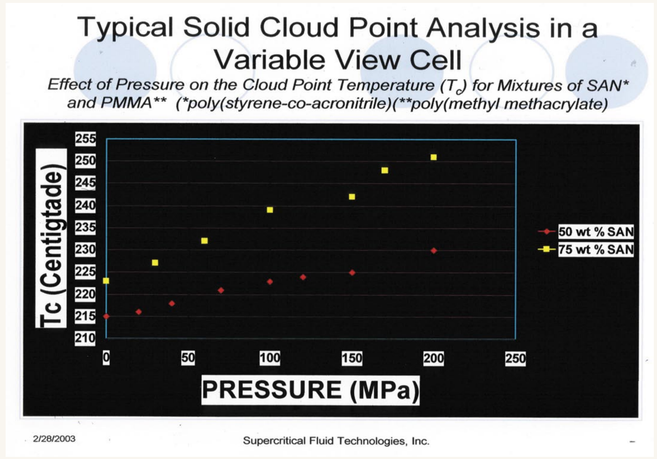

Critical Point


Subcritical state

Critical point of CO_2		
	T_c/ K	P_c/bar
Literature	304.2	73.8
This work	304.1	73.6

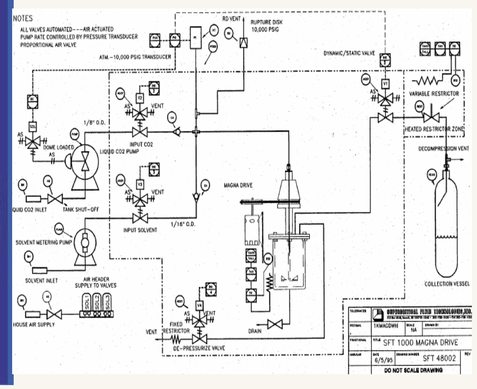
Typical Example of Solubility Parameters Determination

Once the appropriate solubility parameters are obtained for a material at a given temperature, pressure, and co-solvent condition with the Phase Monitor, these data can then applied to give a "starting point"to the development of the true processing parameters in a supercritical fluid extraction unit. Pictured below are some typical cloud point data for the solubility of poly(styrene-co-acronitrile) and poly(methylmethacrylate). When the supercritical fluid and sample is clear, the sample is soluble, when there is a "cloud point"of the supercritical fluid and sample there is no (or minimal) solubility.

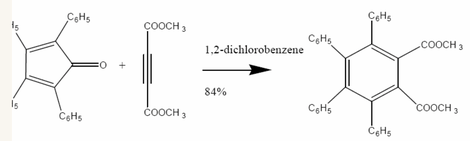


Supercritical Fluid Reaction Development Unit

A typical SFR is comprised of a high pressure carbon dioxide pump, fluid preheater, co-solvent/ reagent addition module(s), high pressure reaction cell, analytical probes for in-situ analysis, mixing, heated micrometeringvalve, atmospheric (or pressurized) collection/separator vessel(s) and flow meter. Reagents can be placed in the high pressure reaction vessel and carbon dioxide and reactants flows into the reactor. The micrometeringvalve depressurizes the supercritical fluid (to the gas state) and the analyte of interest precipitate in the collection vessel.Key reaction processing parameters are investigated to optimize the desired product yield and quality. Preparation of Reagent:Grating, Grinding (cryogrinding), Flaking, Pelletizing, Drying, and Wetting. Reaction Conditions:Pressure, Temperature, Preheater settings, Solvent Selection, Co-solvent Selection (Concentration), Flow Rate, Vessel Aspect Ratio, Solvent/Feed Ratio, and mixing configuration. Separator Conditions:Pressure, Temperature, Adsorbent Separation, Membrane Separation, Filter Separation, Centrifugal Separation, Fractional Separation



Case Study #1 –Diels-Alder Reaction: Synthesis of Dimethylteteraphenylphthalateusing SCF as the Reaction MediumSupercritical fluids are an attractive alternative solvent system to many solvents used in industrial processes, such as methylenechloride,because they can be easily recycled and they provide ease of final product separation. The Diels-Alder reaction was chosen to explore the SCF as a reaction medium. This particular reaction was chosen for a few reasons. First, it is a very useful synthetic reaction resulting in the formation of a six-member ring. Another reason is that the Diels-Alder reaction proceeds under neutral conditions (no acid or base required) making it a good starting point with which to perfect the methodology of the new solvent medium. Thirdly, there is precedent that the Diels-Alder reaction can be adapted to supercritical carbon dioxide. We have observed the successful implementation of the dimethyltetraphenylphthalateDiels-Alder reaction in supercritical carbon dioxide. Further researchwill be performed to optimize the yield for this reaction. It is proposed that the reaction does not go to completion because not all of the starting material is going into solution. The recent acquisition of a new vessel will allow the reaction to be mixed to uniformly distribute the starting materials throughout the vessel. The new vessel will also allow access to a higher temperature. Future plans include the investigation of other Diels-Alder reactions to see if they can also be successfully adapted to the new solvent medium.



Trial	Time (hours)	Pressure (psi)	Equivalence	% yield
1	5	7289	5.646	31
2	5	7487	1.563	44
3	2	7482	1.563	*
4	5	7489	1.563	58
5	5	5299	1.563	22
6	5	4940	1.563	22
7	5	7511	5.646	78**

Case Study #2 –Reaction of Gauifenesin, Dextromethorphan, Phenylephrine, (model compounds) and Dexchlorophenieamine with Tannic Acid –Acid/Base Reaction in Supercritical Fluids.

A typical acid-base reaction used in pharmaceutical industry was performed. The reaction was investigated to determine first if the reaction was possible in SCF's using pharmaceutical model compounds and then to determine thereaction conditions using the actual pharmaceutical grade materials for optimization of yield and %EE. The reactants and products were processed using the Phase Monitor to determinethe solubility data for the materials and screen preliminary reaction conditions and then the reactions were carried out in the SFT-250 SFR Processing Unit.

Model Pharmaceutical Reaction

Gauifenesin+ Tannic Acid, 6000 psi, 70 degrees Celsius, Vigorous Mixing, 3hours: >90% Yield

Gauifenesin+ Tannic Acid, 6000 psi, 90 degrees Celsius, Vigorous Mixing, 3hours: >98% Yield

Dextromethorphan+ Tannic Acid, 6000 psi, 70 degrees Celsius, Vigorous Mixing,3 hours: No Rxn.

Dextromethorphan+ Tannic Acid, 6000 psi, 110 degrees Celsius, Vigorous Mixing,3hours: >95% Yield

Phenylephrine+ Tannic Acid, 6000 psi, 40 degrees Celsius, Vigorous Mixing,3hours: >95% Yield

Pharmaceutical Synthesis

Dexchlorophenieamine+ Tannic Acid, 6000 psi, 85 degrees Celsius, Vigorous Mixing, 3hours: >98% Yield, 100%EE

Scale up operations: 5 gallon SFR pilot plant (SFT-1000 SFR Processing Unit)

Conclusions: The use of supercritical fluids as a reaction media offers thechemical and pharmaceutical industries the opportunity to replace conventional hazardous organic solvents and simultaneously optimize and control more precisely the effect of solvent on reaction. Supercri tical fluids, unlike traditional solvents, can be "pressure tuned"to exhibit gas-like to liquid-like properties. Supercritical Fluids have liquid-like local densities and solvent strength, which can be "tuned"by adjusting the pressure in the reactor in allowing for the control of the solubility of the reactants along with density-dependent properties such as dielectric constant, viscosity, and diffusity. Additionally, solubility control through pressure can allow for easy separation of products and catalysts from the supercritical solvent.