

# Assessing Feasibility of Supercritical Reaction Processes Using Laboratory Equipment

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## Abstract

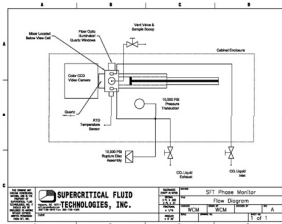
The primary goal of laboratory supercritical fluid reaction unit testing is to assess the technical feasibility of a potential supercritical fluid reaction application. Initial screening with a Phase Equilibrium Analyzer should be carried out to determine the processing conditions in which the reagents and products of interest solubilize and/or precipitate from the supercritical fluid. Experimentation then moves to the use of a supercritical fluid reaction laboratory unit. The laboratory unit typically has a 50 ml 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) Collection Conditions. The reaction product is analyzed to determine how changes in these parameters affect yield, purity and economics of the proposed process. This information can then be utilized to fine-tune the reaction to maximize key parameters for a commercial scale supercritical fluid reaction process. Examples demonstrating the use of both a laboratory SFR unit and a 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. The Phase 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.

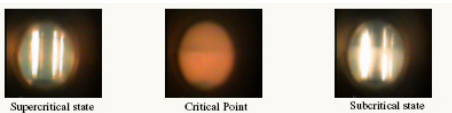
## Variable-Volume Equilibrium View Cell Design

Main components include a Variable-Volume Equilibrium View Cell, Pressure Generator, Light Source and Color CCD Video Camera, Sample Mixing, 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 150° Celsius.



## Validation

The accuracy of the experimental method was validated by comparing the experimentally determined critical point for pure CO<sub>2</sub> with the literature values. The gradual phase transition of carbon dioxide from a single phase supercritical state through the critical point to a two phase subcritical state is pictured below. The view cell shown here has a glass tube inserted in the cell.



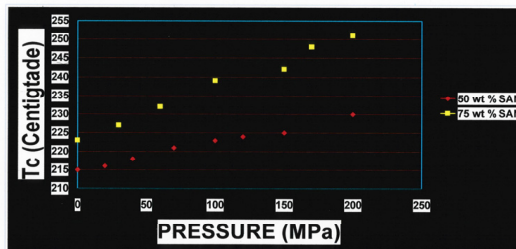
Critical point of CO <sub>2</sub>		
	T <sub>c</sub> /K	P <sub>c</sub> /bar
Literature	304.2	73.8
This work	304.1	73.6

## 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 be applied as 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-acrylonitrile) and poly(methyl methacrylate). When the supercritical fluid and sample is clear, the sample is soluble; and when there is a "cloud point" of the supercritical fluid and sample there is no solubility or minimal solubility.

## Typical Solid Cloud Point Analysis in a Variable View Cell

Effect of Pressure on the Cloud Point Temperature (T<sub>c</sub>) for Mixtures of SAN\* and PMMA\*\* (\*poly(styrene-co-acrylonitrile)\*\*poly(methyl methacrylate)



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## Supercritical Fluid Reaction Development Unit

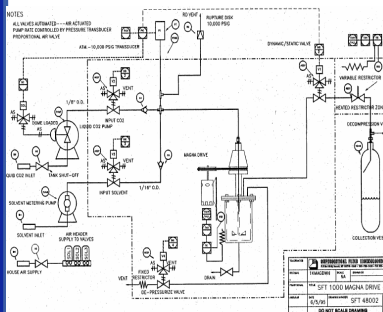
A typical SFR is comprised of a high pressure carbon dioxide pump, fluid preheater, co-solvent/reagent addition module(s), high pressure reaction cell, analytical probes for in-situ analysis, mixing, heated micrometering valve, atmospheric (or pressurized) collection/separator vessel(s) and flow meter. Reagents can be placed in the high pressure reaction vessel and carbon dioxide and reactants flow into the reactor. The micrometering valve depressurizes the supercritical fluid (to the gas state) and the analyte of interest precipitates 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.

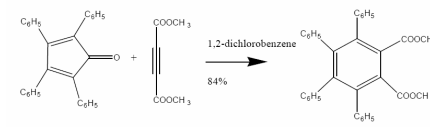
**Separator Conditions:** Pressure, Temperature, Adsorbent Separation, Membrane Separation, Filter Separation, Centrifugal Separation and Fractional Separation



## Case Study #1 – Diels-Alder Reaction: Synthesis of Dimethyltetraphenylphthalate using SCF as the Reaction Medium

Supercritical fluids are an attractive alternative solvent system to many solvents used in industrial processes, such as methylene chloride, 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 dimethyl tetraphenylphthalate Diels-Alder Reaction in supercritical carbon dioxide. Further research will 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 goes into solution. The recent acquisition of a new vessel will allow the reaction to be mixed uniformly, distributing 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 Dextrchloropheniamine 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 the reaction conditions using the actual pharmaceutical grade materials for optimization of yield and %EE. The reactants and products were processed using the Phase Monitor to determine the solubility data for the materials and to screen preliminary reaction conditions. The reactions were then carried out in the SFT-250 SFR Processing Unit.

## Model Pharmaceutical Reaction

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

Dextrchloropheniamine + Tannic Acid, 6000 psi, 85 degrees Celsius, Vigorous Mixing, 3 hours: >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 the chemical and pharmaceutical industries the opportunity to replace conventional hazardous organic solvents and simultaneously optimize and precisely control the effect of solvent on reaction. Supercritical 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 to allow for the control of the solubility of the reactants along with density-dependent properties such as dielectric constant, viscosity and diffusivity. Additionally, solubility control through pressure allows for easy separation of products and catalysts from the supercritical solvent.