



# Interfacing supercritical fluid reaction apparatus with on-line liquid chromatography: Monitoring the progress of a synthetic organic reaction performed in supercritical fluid solution



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## ABSTRACT

An interface has been developed that connects a supercritical fluid reaction (SFR) vessel directly on-line to a liquid chromatograph. The combined SFR-LC system has enabled the progress of the esterification reaction between phenol and benzoyl chloride to synthesize phenyl benzoate in supercritical fluid carbon dioxide solution to be dynamically monitored. This was achieved by the periodic SFR-LC analysis of samples directly withdrawn from the esterification reaction mixture. Using the series of SFR-LC analysis results obtained for individual esterification reactions, the reaction progress profile for each esterification reaction was obtained by expressing the measured yield of phenyl benzoate as a function of reaction time. With reaction temperature fixed at 75 °C, four sets ( $n=3$ ) of SFR-LC reaction progress profiles were obtained at four different SFR pressures ranging from 13.79 to 27.58 MPa. The maximum SFR yield obtained for phenyl benzoate using a standard set of reactant concentrations was 85.2% (R.S.D. 4.2%) when the reaction was performed at 13.79 MPa for 90 min. In comparison, a phenyl benzoate yield of less than 0.3% was obtained using the same standard reactant concentrations after 90 min reaction time at 75 °C using either: heptane, ethyl acetate or acetonitrile as conventional organic reaction solvents.

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## 1. Introduction

Environmentally damaging, toxic and relatively expensive organic solvents are extensively used in synthetic manufacturing processes. These solvents are often destroyed by incineration once they can no longer be purified and recycled and this contributes to carbon dioxide emissions as well as hazardous transportation issues. It is well established that: non-toxic, non-flammable, non-corrosive, odorless, inexpensive, inexhaustible, ubiquitous, and low disposable cost carbon dioxide in its supercritical fluid state can be manipulated *via* density control to imitate a range of non-polar organic solvents [1,2]. With careful consideration [3] this potentially makes supercritical fluid carbon dioxide (SF-CO<sub>2</sub>) an attractive option in appropriate circumstances to replace or partially replace the use of some organic solvents widely used for synthetic manufacturing processes. In addition, synthetic reactions that can be conducted in supercritical fluid solution may proceed at significantly faster reaction rates compared to what is achievable using conventional organic reaction solvents [4]. This is generally

attributed to more efficient mass transfer occurring in supercritical fluids whose physical state characteristically provides lower viscosities than liquids. At the end of SFR synthetic procedures involving the use of SF-CO<sub>2</sub>, carbon dioxide can be conveniently expanded to waste compared to energy demanding organic solvent removal processes that are generally required to isolate products prepared using conventional synthetic procedures. Alternatively, depending upon the scale of the SF-CO<sub>2</sub> process, it is possible to recycle decompressed carbon dioxide following its purification and recompression.

Due to the potential benefits, a wide range of synthetic organic reaction procedures using SF-CO<sub>2</sub> as reaction solvent have been developed [5–9]. Despite this, the use of SF-CO<sub>2</sub> as an alternative solvent for synthetic reactions has not yet been widely adopted. In order to help further advance the development and optimization of synthetic procedures performed in supercritical fluid solution it is advantageous to monitor SFR processes on-line. Development of on-line process analytical technology (PAT) although being relatively new continues to evolve across various manufacturing sectors [10,11]. This involves a range of applications, particularly within the pharmaceutical industry [12–16] where rapid process development and optimization for the manufacture of high value products is of key importance. Real time or near time PAT is

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differentiated from off-line laboratory techniques in that it typically provides process analysis results in seconds to minutes as opposed to hours or days. The majority of PAT procedures currently introduced or being developed for applications involving conventional solvent based synthetic organic chemistry utilize different types of on-line spectroscopic techniques [17,18]. However, on-line HPLC has also been used for the development of synthetic organic reactions performed in conventional solvents [19–21].

Only very few reports have described the use of PAT with synthetic organic chemistry SFR equipment. These PAT studies have involved the on-line coupling of spectroscopic techniques [22–24]. Although less rugged than PAT spectroscopic instrumentation, on-line chromatographic procedures are well suited for SFR feasibility studies and small-scale SFR process development studies that may result in a mixture of products being formed. Additionally, chromatography based PAT procedures provide potential for the rapid detection of unexpected by-products particularly at trace levels. Liquid chromatography is currently established as the dominant chromatographic technique used in the pharmaceutical industry. Accordingly, the principle objective of this study was to develop a near time PAT method for small scale SFR apparatus using on-line liquid chromatography.

The interfacing of supercritical fluid extraction (SFE) systems, which utilize SFR type vessels, with liquid chromatography has been reviewed [25–27]. With coupled SFE–LC instrumentation, intermediate sorbent traps are often used to collect and pre-concentrate extracts prior to LC analysis. Intermediate SFE–LC sorbent traps generally require the use of solvent flushing stages to transfer trapped extracts for analysis whilst preventing decompressed gas from being introduced into the HPLC system. Such sorbent trap arrangements have typically involved the use of either a ten port valve [28,29] or multi valve SFE–LC interface [30,31]. A simplified SFE–LC interface that utilizes a single six port valve with an analyte sorbent trap has also been developed [32].

This report describes the use of a two valve interface that enables the direct on-line coupling of SFR apparatus to a liquid chromatograph. The SFR–LC interface does not utilize an intermediate sorbent trap which simplifies its mode of operation and facilitates higher sampling rates making it more suitable for near time PAT applications. The SFR–LC interface design ensures that a representative sample of reaction mixture dissolved in supercritical fluid solution is rapidly withdrawn from within the SFR vessel for direct on-line liquid chromatographic analysis. Using SFR–LC, the progress of the esterification reaction between phenol and benzoyl chloride to synthesize phenyl benzoate in SF-CO<sub>2</sub> was studied. In order to compare SFR performance with respect to reaction rate and product yield, the same esterification reaction was also conducted in three different aprotic conventional organic reaction solvents of different polarity.

## 2. Experimental

### 2.1. Materials and reagents

Analar grade: phenol, benzoyl chloride, methyl benzoate, phenyl benzoate, and biphenyl were obtained from ACROS Organics (Shanghai, China). HPLC grade methanol and water were obtained from Sigma-Aldrich (Shanghai, China). Analar grade heptane, ethyl acetate and acetonitrile were obtained from Dikma Technologies (Beijing, China). SFR–LC interface chromatographic performance measurements were performed using: (i) the SFR vessel loaded with 20  $\mu$ L methyl benzoate, 20 mg phenyl benzoate and 10 mg biphenyl dissolved *in situ* using SF-CO<sub>2</sub>, and (ii) a standard solution composed of 20  $\mu$ L methyl benzoate, 20 mg phenyl benzoate and 10 mg biphenyl dissolved in 25 mL ethanol. All SFR–LC

esterification reaction studies involved the use of a 2:1 mole excess of phenol to benzoyl chloride. This was achieved by initially loading 36 mg phenol and approximately 5 mg biphenyl into the SFR vessel after which 20  $\mu$ L benzoyl chloride was injected into the SFR vessel at various pre-pressure values as described in Section 2.4.

### 2.2. SFR system

A 25 mL SFE vessel obtained from Thar Designs (Pittsburgh, PA, USA) served as the SFR vessel. The original SFE vessel design was modified such that the sintered high pressure seal retainers were replaced with low dead volume direct feed through retainers. The SFR vessel was loaded with a close fitting ceramic marble. The SFR vessel was locked in an AT-330 column oven (Auto Science, Tianjin, China) whose temperature was maintained at 75 °C. A Gilson 307 pump (Middleton, WI, USA) whose pump head was cooled to –15 °C *via* a NESLAB RTE-110 recirculator (Newington, NH, USA) was used to supply liquid carbon dioxide for all supercritical fluid solubility and SFR–LC studies. The cylinder containing 99.999% pure liquid carbon dioxide (AIRICHEM, Dalian, China) was equipped with a liquid draw-off tube.

### 2.3. SFR–LC interface

The SFR–LC interface was constructed using two Rheodyne 7010 valves (Cotati, CA, USA). The valves were mounted on the door of a Gilson 831 oven whose temperature was maintained at 75 °C. The sequence of key SFC–LC interface valve settings to make a sample injection are shown in Fig. 1. The sample injection valve was fitted with a 10  $\mu$ L sample loop whereas the sample draw through valve was fitted with a 250  $\mu$ L loop when standard solutions were formed *in situ* within the SFR vessel and a 650  $\mu$ L loop for SFR–LC studies. During sample loading, a pressurized stream of SF-CO<sub>2</sub> solution from within the SFR vessel rapidly flows through the sample injection valve loop to fill the loop of the draw through valve. After sample injection, the aliquot of supercritical fluid solution held in the draw through valve loop was exhausted to atmosphere *via* a solvent wash system. At the end of completed SF-CO<sub>2</sub> solubility or SFR–LC experiments, the SFR–LC interface was cleaned. The procedure involved disconnecting the SFR vessel and replacing the blank pin on port 3 of the draw through valve with a length of open tubing that discharged into a beaker. A syringe loaded with ethyl acetate was then connected to the line that had been used to connect the SFR vessel to the SFR–LC interface sample injection valve. Using the series of valve switch positions shown in Fig. 1, the SFR–LC interface was cleaned by flushing with several 5 mL aliquots of ethyl acetate. The cleaned SFR–LC interface was then dried *in situ* using a flow of warm gaseous carbon dioxide. During disconnection from the SFR–LC interface, the SFR vessel and ceramic marble were cleaned by sonication in ethyl acetate and then thoroughly dried. After cleaning and drying, the SFR vessel and SFR–LC interface were reconnected and port 3 of the sample draw through valve was refitted with the blank pin. The complete cleaning and reconnection process could be accomplished within 25 min.

### 2.4. SFR system operation and SFR–LC sample injection protocol

Phenol, phenyl benzoate and biphenyl samples were introduced into the SFR vessel on weighing boats made from thin aluminum foil whereas methyl benzoate was directly introduced into the open SFR vessel using a 25  $\mu$ L syringe. Prior to the start of liquid carbon dioxide delivery, the loaded and sealed SFR vessel was allowed to thermally equilibrate for 30 min using an oven temperature of 75 °C. The SFR vessel reached final selected operational target pressure *via* a Gilson 307 pump that utilized two flow rate programs. The first program provided a liquid carbon dioxide flow at 5 mL min<sup>–1</sup>

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