Measurement of Solubility of Ibuprofen and Flurbiprofen Enantiomers in Carbon Dioxide Mobile Phase with Iso-propanol and sec-Butanol as a Modifier

Wade Mack, Brandon Smeltzer, Sermin G. Sunol, Aydin K. Sunol. University of South Florida, 4202 E. Fowler Ave., Tampa, FL 33620

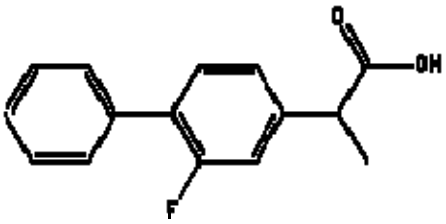
Abstract

Separation of chiral isomers of ibuprofen and flurbiprofen, non-Steroidal Anti-Inflammatory Drugs (NSAIDs) is performed using a sub- and supercritical fluid chromatographic system. Carbon dioxide is used as a mobile phase with iso-propanol and sec-butanol employed as a modifier. For modeling these systems, solubility information is crucial. The solubility of each compound is determined using a phase analyzer from Thar Technology. Cloud points of ibuprofen and flurbiprofen are determined in pure supercritical carbon dioxide and mixtures of carbon dioxide and the alcohol modifier. Cloud point measurements are performed at different operating temperatures and pressures. The results are modeled using PRSV and extended to other experimental conditions.

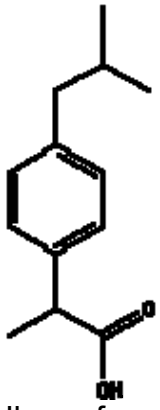
Introduction

Supercritical fluids possess interesting and industry applicable characteristics that set them apart from typical solvents. The lack of surface tension, the mobility of a gas, and the solvation power of a liquid are three unique properties that make supercritical fluids very attractive as tunable solvents (McHugh & Krukonis 1986). Supercritical fluids can be used for the selective recovery (i.e. separation) of solutes by adjusting pressure and temperature.

One engineering field where supercritical fluid selectivity can have a major economic impact is chiral drug separation. Chiral drug separation is an important part of the pharmaceutical industry because some drug isomers are inactive for treatment or even harmful to human health. Two such drugs that are isomeric are 2-fluro-α-methyl[1,1'-biphenyl] 4-acetic acid (flurbiprofen) and alpha-p-isobutylphenylpropionic acid (ibuprofen). Flurbiprofen and ibuprofen belong to a class of drugs called non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are used to reduce inflammation and pain associated with disorders in the muscular and skeletal systems like rheumatoid arthritis, juvenile arthritis, fever, and minor aches (Mosby's Drug Consult). The R and S isomers of both flurbiprofen and ibuprofen have specific applications, so purity of each is important.



Flurbiprofen



Ibuprofen

In order to achieve the separation of the flurbiprofen and ibuprofen isomers in a supercritical fluid, the solubility of each racemic mix is crucial. The solubility of each drug in the supercritical fluid is needed so the proper amount of solvent at a desired operating condition can be used to separate a particular concentration of the drug isomers.

Solubility Determination

The solubility of each NSAID racemic mix was determined using a static variable volume solubility cell purchased from Thar Technologies. The solubility cell volume can be adjusted from 5 ml to 15 ml. The operating pressure and temperature limits monitored by the controller are 413 bar and 150°C, with an error of ± 0.1 bar and ± 0.1°C, respectively. Figure 1 shows the experimental set-up in its entirety:

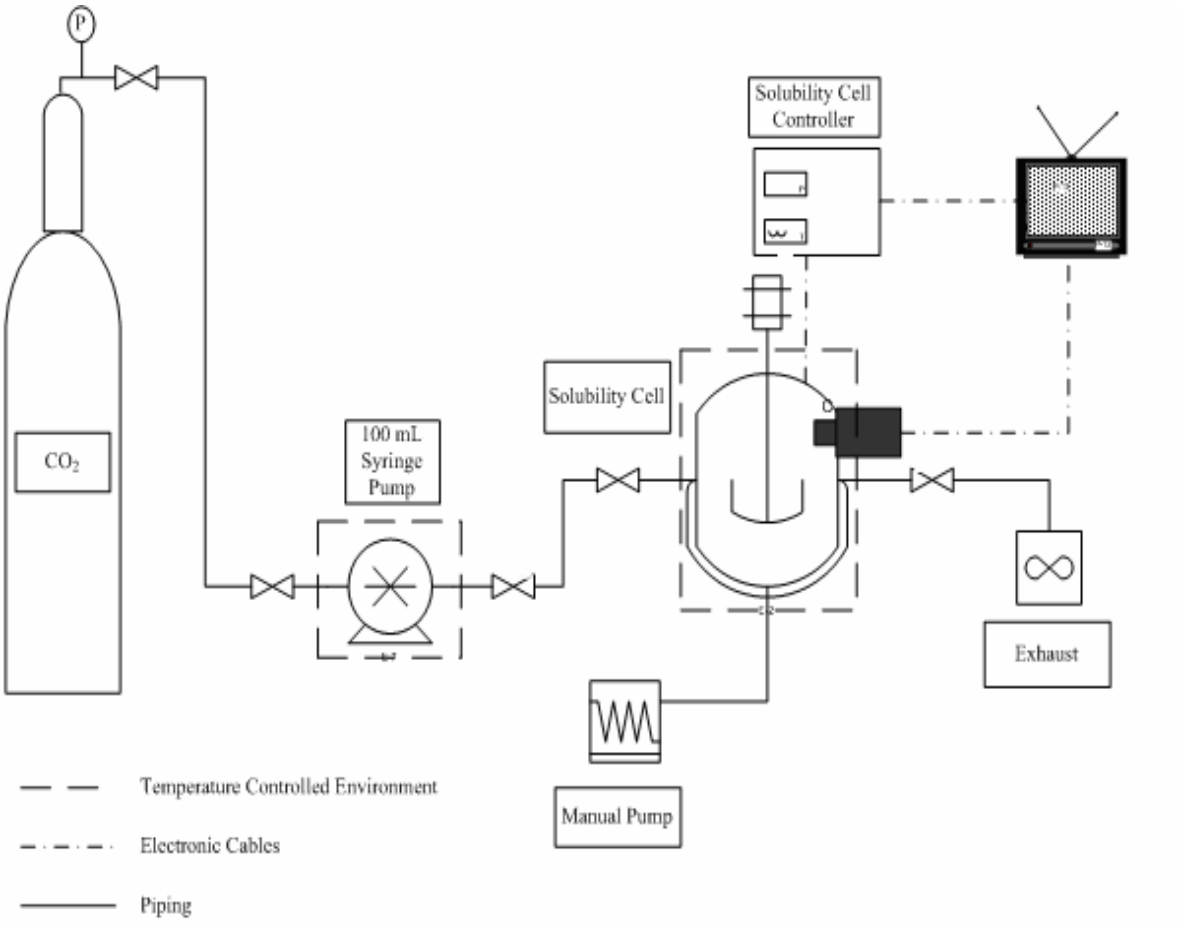


Figure 1. Experimental Set-Up

Carbon dioxide is pumped into an Isco 100DX Syringe Pump. A Lauda Econoline Low-Temperature Thermostat RE120 cools syringe pump to –3°C by circulating antifreeze. The cooling of the syringe pump is done to ensure that the carbon dioxide is in the liquid phase when it is pumped into the solubility cell. The NSAID, Ibuprofen or Flurbiprofen (Aldrich) is weighed and then transferred to the open solubility cell. HPLC grade iso-propanol or sec-

butanol(Aldrich), the entrainer, is weighed in a beaker and transferred to the solubility cell. The entrainer beaker is reweighed and recorded.

The solubility cell is then brought to a minimum volume using a Ruska manual pump while still open. Adjusting the solubility cell to a minimum volume is done so that the presence of air can be considered negligible. The solubility cell is then sealed with the magnetic stirrer. Low-pressure carbon dioxide is pumped into the solubility cell while the outlet valve is open to vacate the solubility cell of air completely. The outlet valve is closed and liquid carbon dioxide is pumped into the solubility cell. Once liquid carbon dioxide is visible on the television, the solubility cell volume is slowly expanded to its maximum volume. Liquid carbon dioxide flow into the solubility cell is shut off when the pressure inside the solubility cell increases one to two bars per second.

The pressure inside the solubility cell is allowed to reach equilibrium. After five to ten minutes, the initial pressure and temperature are recorded. The solubility cell is then shifted to a horizontal position such that the liquid-liquid interface is visible in the camera view cell. The magnetic stirrer is turned on to achieve homogeneity and the solubility cell is heated to temperature ($35^{o}C$, $40^{o}C$, $45^{o}C$, $50^{o}C$) with the controller and heating element. Once the mixture reaches the experiment temperatures listed above the magnetic stirrer is turned off. A Ruska manual pump then pressurizes the solubility cell by forcing an incompressible fluid (deionized water) to move the piston inside the variable volume solubility cell. Pressurization continues until a cloud is observed in the view cell and the mixture becomes clear again with no discernable liquid-liquid interface. This procedure is continued until five cloud point pressures have been recorded at the experiment temperature. When the mixture is heated from one experimental temperature to the next experimental temperature the magnetic stirrer is turned on.

In between each experiment to determine metal complex solubility in supercritical carbon dioxide, the solubility cell undergoes a detailed cleaning process. The cleaning process is necessary to ensure that no contamination occurs in subsequent runs. After sufficient data points have been collected at experimental temperatures the heating element is turned off and the cell is returned to a vertical position. The outlet valve of the solubility cell is opened such that depressurization occurs at approximately two to three bars per minute. The slow depressurization rate is necessary to prevent clogging in the outlet valve and line.

Once pressure inside the solubility cell is completely released, the magnetic stirrer is unsealed from the top of the machine. The solubility cell is then inverted 180^{o} to remove the rest of the experimental mixture. The camera, inlet and outlet valves, thermocouple, and light are unplugged from the solubility cell. The solubility cell is then unscrewed from the base of the Supercritical Phase Analyzer. The two o-rings on the bottom of the solubility cell are removed and rinsed thoroughly with deionized water followed by denatured ethanol (Fischer). The o-rings are then allowed to air-dry.

The frit on the movable piston is unscrewed next. The frit is washed thoroughly with deionized water followed by denatured ethanol. The frit is then allowed to air-dry. The piston is rinsed with deionized water followed by denatured ethanol, wiped dry. The piston is then allowed to air-dry.

The stirrer is removed from the magnetic stirrer and rinsed thoroughly with deionized water followed by denatured ethanol. The stirrer is then allowed to air-dry. The solubility cell cap that houses the stirrer is rinsed thoroughly with deionized water followed by denatured ethanol. The solubility cell cap is then allowed to air-dry.

The solubility cell is rinsed thoroughly with deionized water followed by denatured ethanol. The solubility cell is then allowed to air-dry. Air-drying times for all components were a minimum of ten minutes.

After air-drying is complete, the solubility cell components are reassembled. A second cleaning is done at this point with pure carbon dioxide. Liquid carbon dioxide is pumped into the solubility cell, which is at its maximum volume. The flow of liquid carbon dioxide is shut off once the solubility cell is full as evident from pressure increases of one to two bars per second noted on the controller. The magnetic stirrer is turned on to improve cleaning efficiency. This solubility cell cleaning process with liquid carbon dioxide continues for ten minutes, then the solubility cell is depressurized two to three bars per minute.

After the pure carbon dioxide cleaning process, the magnetic stirrer and the solubility cell are removed from the Supercritical Phase Monitor and once again allowed to air-dry.

Results

Both ibuprofen and flurbiprofen racemic mixtures are soluble in supercritical carbon dioxide alone. However, the cloud point pressures are well above 100 bars at temperatures ranging from 35^{o}C to 50^{o}C. The addition of iso-propanol as an entrainer greatly increases the solubility of ibuprofen in supercritical carbon dioxide at lower pressures. Cloud points for carbon dioxide-isopropanol-ibuprofen ternary system have been observed around 100 bars at various ibuprofen concentrations. The same general phenomena have been observed using sec-butanol as the entrainer as well.

Flurbiprofen is soluble in supercritical carbon dioxide alone as well, however the addition of an entrainer such as iso-propanol or sec-butanol greatly increases the amount of flurbiprofen that can be solubilized in supercritical carbon dioxide. Cloud point pressures for both entrainers have also been determined around 100 bars for temperatures ranging from 35^{o}C to 50^{o}C.