

Measurement of Aqueous Solubility of Compounds at High Temperature

Using a Dynamic Flow Apparatus and a Teledyne ISCO Syringe Pump

Jerry W. King & Keerthi Srinivas, University of Arkansas, Dept. of Chemical Engineering



Syringe Pump Application Note AN27

Introduction

Flavonoids are a diverse group of polyphenolic compounds present in plants, which have antioxidant, anti-bacterial, anti-carcinogenic and anti-inflammatory properties [1]. Carbohydrates such as glucose, xylose, and maltose are extensively used not only as sweeteners and additives in food industries but also as intermediates in biofuel production [2]. Knowledge of the temperature-dependent aqueous solubilities of such compounds in conjunction with other physicochemical data such as diffusion coefficients can significantly aid in understanding and optimizing their extraction from natural products which have applications in food, pharmaceutical and bioenergy industries. However, such data is limited and, in most cases, non-existent in literature. The solubility of the above compounds in water cannot be accurately measured using traditional static methods, especially near or above the boiling point of the solvent, due to the molecular complexity and sensitivities of these compounds to light, heat, and oxygen. A dynamic flow apparatus was constructed to allow the solvent (water, in this case) to flow over the pure com-

pound packed in a saturation cell placed in a constant temperature oven. This dynamic solubility measurement method can accurately measure the aqueous solubility of such thermally-labile compounds at temperatures near or higher than the boiling point of water. Such a system requires a very precise constant flow rate be maintained under elevated pressures and temperature.

Because the dynamic flow apparatus measures the aqueous solubility in subcritical water conditions, the system requires sufficient pressure to maintain water in its liquid state above its boiling point as shown in phase diagram of water shown in Figure 1. This requirement can range from a few atmospheres between 100 -160° C to 30 - 40 atmospheres at temperatures ranging from 150 -200° C. Such conditions can be achieved by employing a Teledyne ISCO syringe pump coupled with a back pressure regulator for precise flow control (including incorporation of a second Teledyne ISCO syringe pump for sample dilution) as described below.

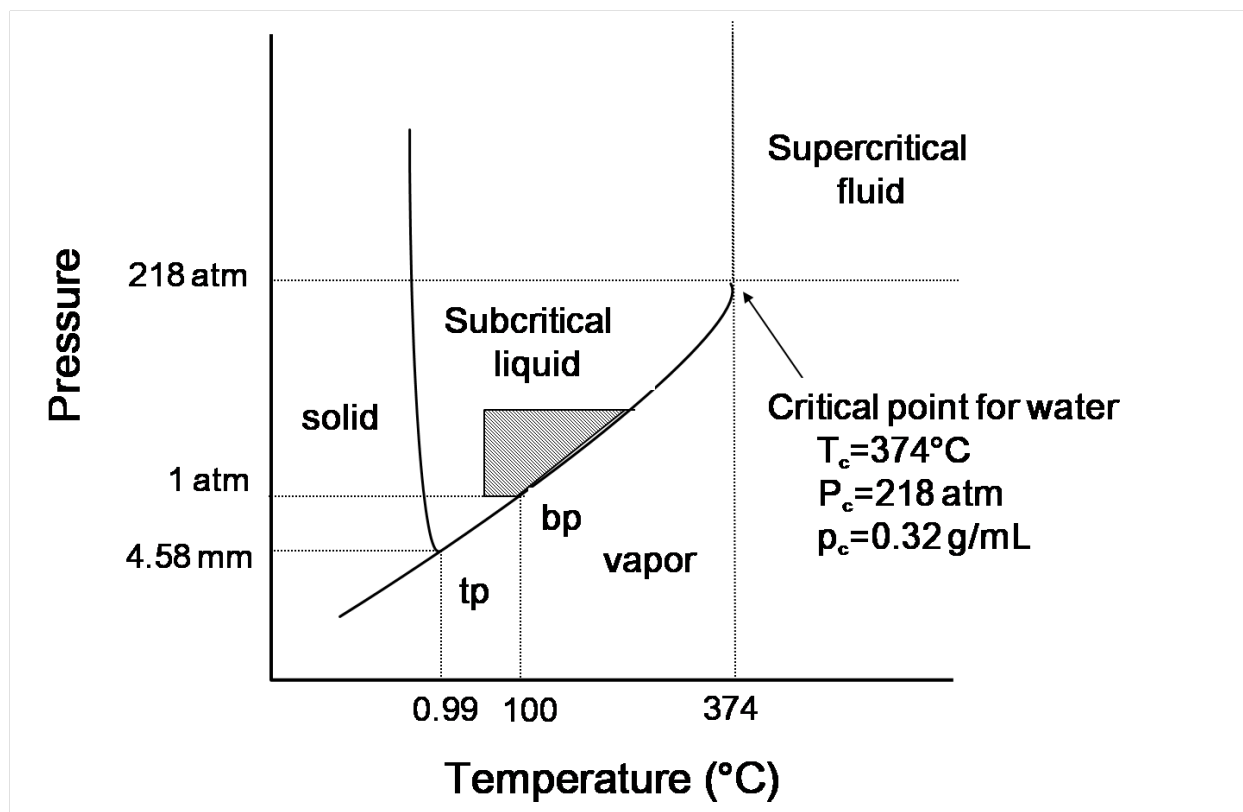


Figure 1: Phase diagram of water showing vapor-liquid relationship for subcritical water

Experimental Procedure

The experimental apparatus for measuring the aqueous solubilities of the compounds as a function of temperature was based on a modification of the system used by Miller and Hawthorne [3]. The system was comprised of two Teledyne ISCO 260D high precision syringe pumps (Teledyne ISCO, Lincoln, NE) used to supply water (solvent) in a constant flow mode [see note]. The solubility measurements were conducted at a constant temperature using a Hewlett Packard Model 5890 oven [4-6]. The oven temperatures were accurately measured using a J-thermocouple coupled to an Omega DP703 thermocouple microcomputer (Stamford, CT, USA). Water from a storage reservoir flowed through a Teledyne ISCO 260D syringe pump through a preheating coil and contacted an excess amount of the compound in a saturation cell placed in the constant temperature oven. The compound dissolved in water (at the set experimental temperature) further contacted the excess water, which was dispensed using a second Teledyne ISCO 260D syringe pump held inside the oven. The two flows were mixed in a “T” (High Pressure Equipment Inc. (HIP), Eric, PA, P/N# HIP15-23AF1) held inside the oven. The flow rates in both the Teledyne ISCO

syringe pumps were controlled using a Teledyne ISCO SFX 200 controller (Lincoln, NE, USA) [see note]. The solvent flow rate in the first Teledyne ISCO pump was varied depending on the experimental temperature, and the flow rate in the second Teledyne ISCO pump was set to maintain a dilution factor of 4. The excess water was used to make sure the compound remained solubilized in solution as the mixture exited the oven to ambient temperature, thus preventing the precipitation of the dissolved solute in the tubing. After exiting the oven, the mixture flowed through a cooling coil via an on/off switching valve (High Pressure Equipment Inc. (HIP), Eric, PA; P/N # HIP15-11AF1) and into a sampling vial for quantification of solute concentration using high performance liquid chromatography (HPLC). The switching valve was used to prevent the flashing of water to steam as the mixture exited the oven. The system pressure varied between 1 atm at temperatures up to 353 K and as high as 3.5 atm at higher temperatures; these were sufficient pressures to sustain water above its boiling point in the subcritical state. The experimental solubility apparatus is shown in Figure 2.

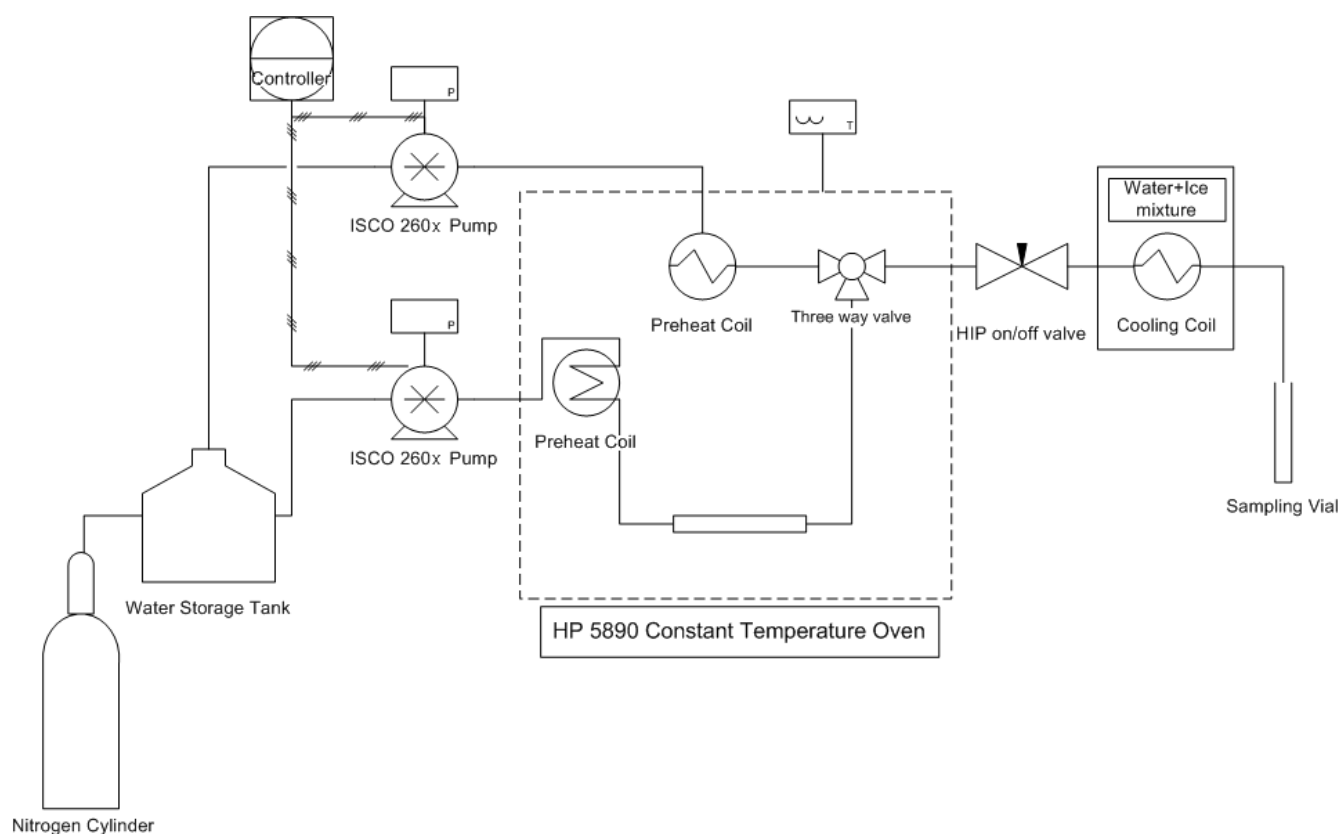


Figure 2: Dynamic flow apparatus for measuring the aqueous solubility of compounds as a function of temperature above and below the boiling point of water

The concentration (g/L) of the compound in water increased as a function of time at a set experimental temperature until it reached a saturated value determined by the solubility of the compound in water at the

experimental temperature. The aqueous solubility of the compound in g/L units was converted to mole fraction units using the following equation:

$$x_s (\text{mole fraction}) = \frac{1}{1 + \left[\frac{M_s}{M_w} * \left(\frac{1}{S(\text{g/L})} - 1 \right) \right]} \quad (1)$$

Results and Discussion

The above dynamic flow apparatus was used to measure the aqueous solubility of sugars and flavonoids as a function of temperature. The solubility of the flavonoids and sugars in water was found to increase exponentially as a function of temperature. The exponential increase in the solubility of sugars as a function of temperature is shown in Figure 3. While the sugar solubilities varied between 463 g/L at 298 K to 4240 g/L at 456 K for xylose, the lowest aqueous solubility measured for flavonoids

ranged between 0.00215 g/L at 299 K and 0.666 g/L at 416 K for anhydrous quercetin. The aforementioned values indicate the large dynamic range of the aqueous solubility of these compounds that can be measured using the dynamic flow apparatus. The size of the saturation cell varied depending on the increase in solubility of the selected compounds in water as a function of temperature.

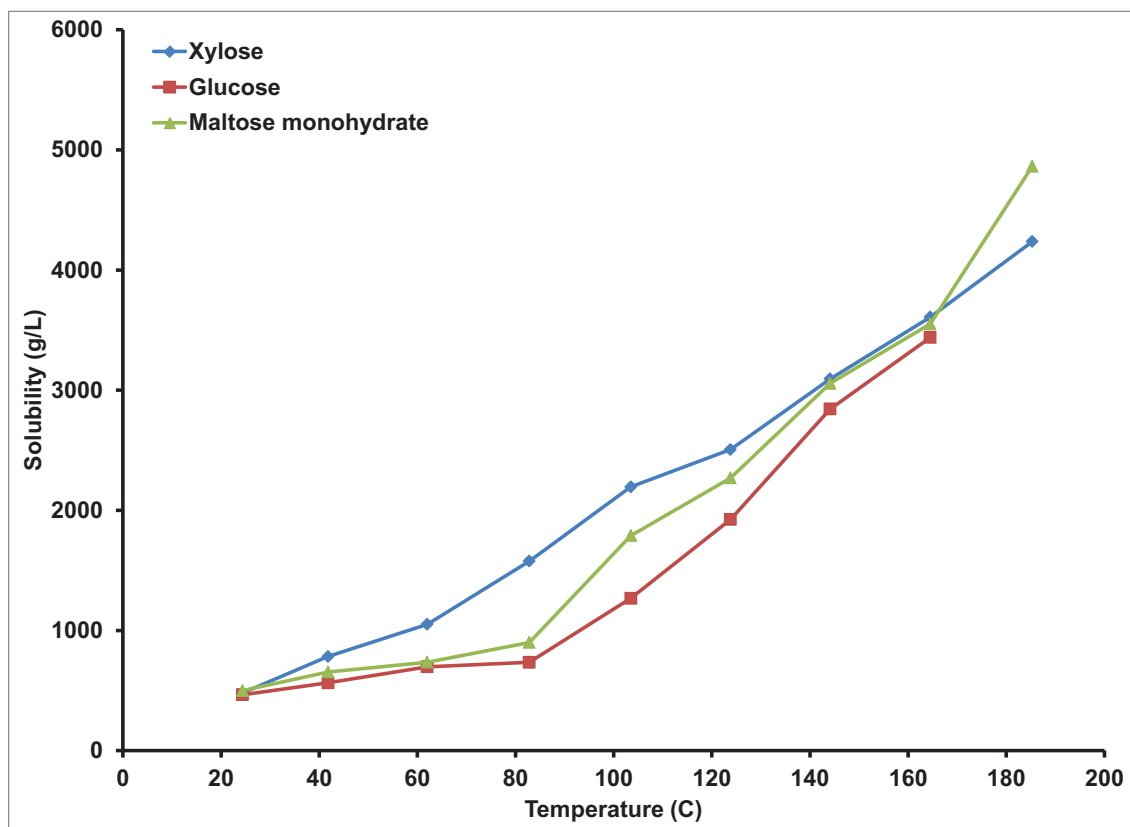


Figure 3: Aqueous solubility of sugars as a function of temperature

The dynamic flow apparatus was also used to measure the aqueous solubility of quercetin in its anhydrous form and as its dihydrate as a function of temperature (Figure 4). It can be seen from Figure 4 that the dynamic flow apparatus utilizing a high precision Teledyne ISCO syringe pump can be used to measure the onset of the

polymorph transformation temperature of organic compounds such as quercetin. Such data is useful in the pharmaceutical industries to indicate the temperature above which an anhydrous form of a compound has a higher aqueous solubility than its hydrated form. Such a transition occurs for quercetin at 393 K. Above this tem-

perature, the aqueous solubility of quercetin dihydrate in grams per liter units was almost twice that of anhydrous quercetin, but their aqueous solubility expressed in mole fraction units shows the inverse trend. This is due to the presence of two molecules of water in quer-

cet in dihydrate which increases the molecular weight of the dihydrate relative to quercetin.

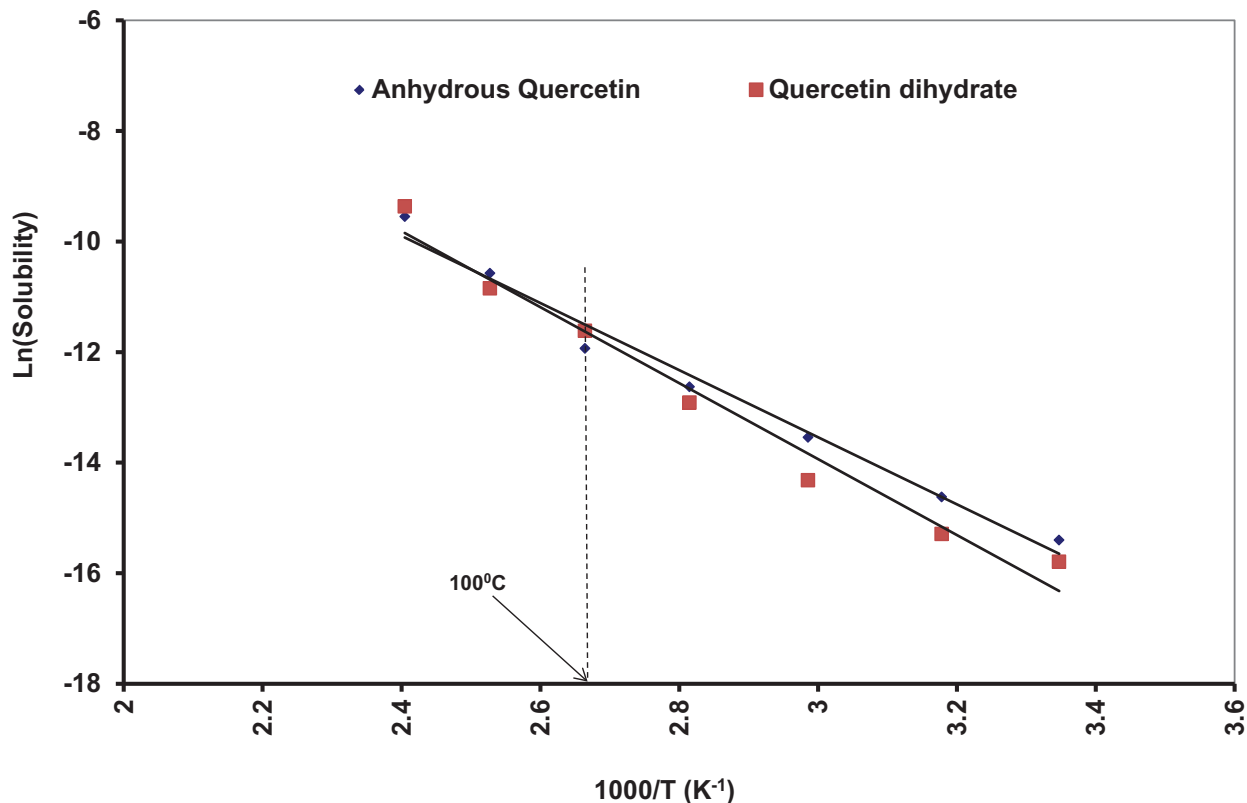


Figure 4: Variation of natural logarithm of the aqueous solubility (mole fraction) of anhydrous quercetin and quercetin dihydrate with reciprocal of temperature

Studies indicated that solubility measurements using the dynamic flow apparatus at a constant flow rate of 0.1 mL/min showed degradation of flavonoids above 353 K and of sugars above 413 K. In the case of sugar solutes, there was evidence of charring inside the saturation cell which resulted in the dark color of the collected extracts. Studies reported in the literature indicated dehydration of sugars [7] and flavonoids [8] when heated over prolonged periods of time over 373 K and 353 K respectively. This problem was overcome by increasing the solvent flow rate through the saturation cell. The solvent flow rate in the dilution pump was also increased appropriately to maintain a minimum dilution factor of 4. The flow precision affected by using the two Teledyne ISCO syringe pumps makes such an adjustment possible. The effect of solvent flow rate on the aqueous solubility of quercetin dihydrate at 373 K and 413 K is shown in Figure 5 (a, b).

At 373 K, it can be seen that there is a minimal effect (no statistical significance at 95% confidence interval) of flow rate on the aqueous solubility of quercetin dihydrate (Figure 5a). However, at 413 K, it can be seen that

at solvent flow rates of 0.1 and 0.2 mL/min, there is a rapid decrease in the concentration of quercetin dihydrate plotted as a function of time until it reaches a zero value. It can be observed that the concentration profile drops to zero faster when the solvent flow rate is 0.1 mL/min relative to that at 0.2 mL/min. At such temperatures (413 K), it was found that a higher solvent flow rate of 0.5 mL/min helped maintain thermal stability of the compounds and increased the accuracy of the reported solubility values. Using these conditions, the sugar degradation was also minimized as judged by the disappearance of additional peaks in the HPSEC profile, since only the peak of the carbohydrate solute was observed in the HPSEC profile when using refractive index detection.

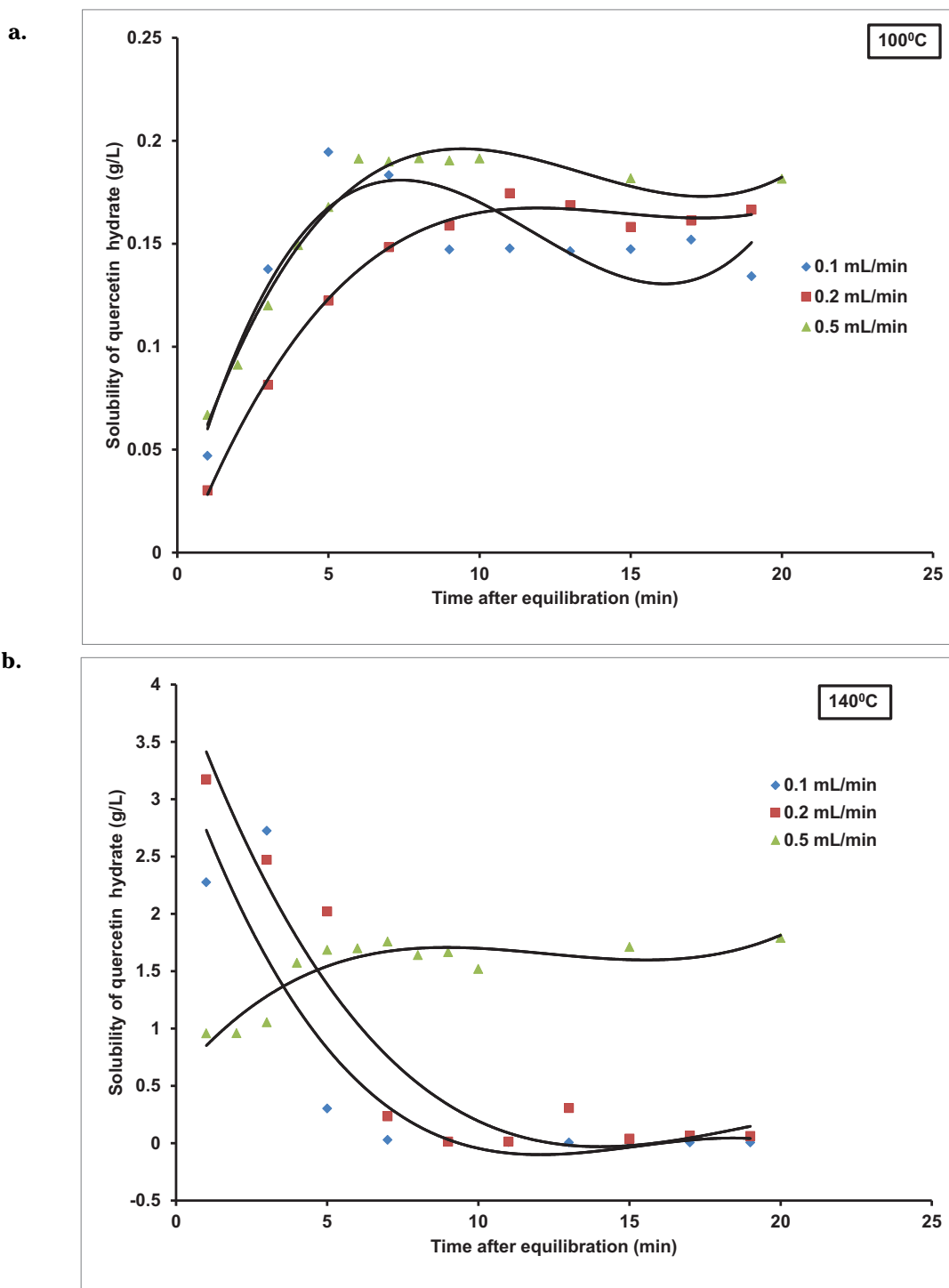


Figure 5: Concentration profile of quercetin dihydrate as a function of solvent flow rate at: (a) 373 K; and (b) 413 K

In the case of flavonoids at low solvent flow rates (0.1 mL/min) and higher temperatures (413 K), it was found that the saturation cell was still sufficiently packed at the end of the experiment. However, after the experiment, the solid mass in the saturation cell was found to be harder and agglomerated. This agglomeration of the quercetin dihydrate due to the combined

effect of flow rate and temperature was seen through the changes in pump pressure as recorded by the Teledyne ISCO SFX 200 controller (Figure 6). It can be seen from Figure 6 that at 413 K and a 0.1 mL/min solvent flow rate, the pump pressure was drastically reduced from its initial value indicating an uninterrupted flow through the saturation cell, while a solvent flow rate of 0.5 mL/min at

the same temperature showed a consistent stability in the pump pressure. This decrease in the recorded pump pressure along with a decreased concentration profile and unchanged mass of packing in the saturation cell can be attributed to the agglomeration of the quercetin dihydrate in the cell due to thermal dehydration of the compound. This effect was confirmed by taking scanning electron microscopic (SEM) images on pure quercetin dihydrate both before (Figure 7a) and after

experiments conducted at 413 K (Figure 7b). Adjustment of the ratio of the water flow rate to the saturation cell dilution pump is critical in optimizing the reported method and will depend on the thermal stability of the solute under examination at the chosen temperature for the solute solubility measurement.

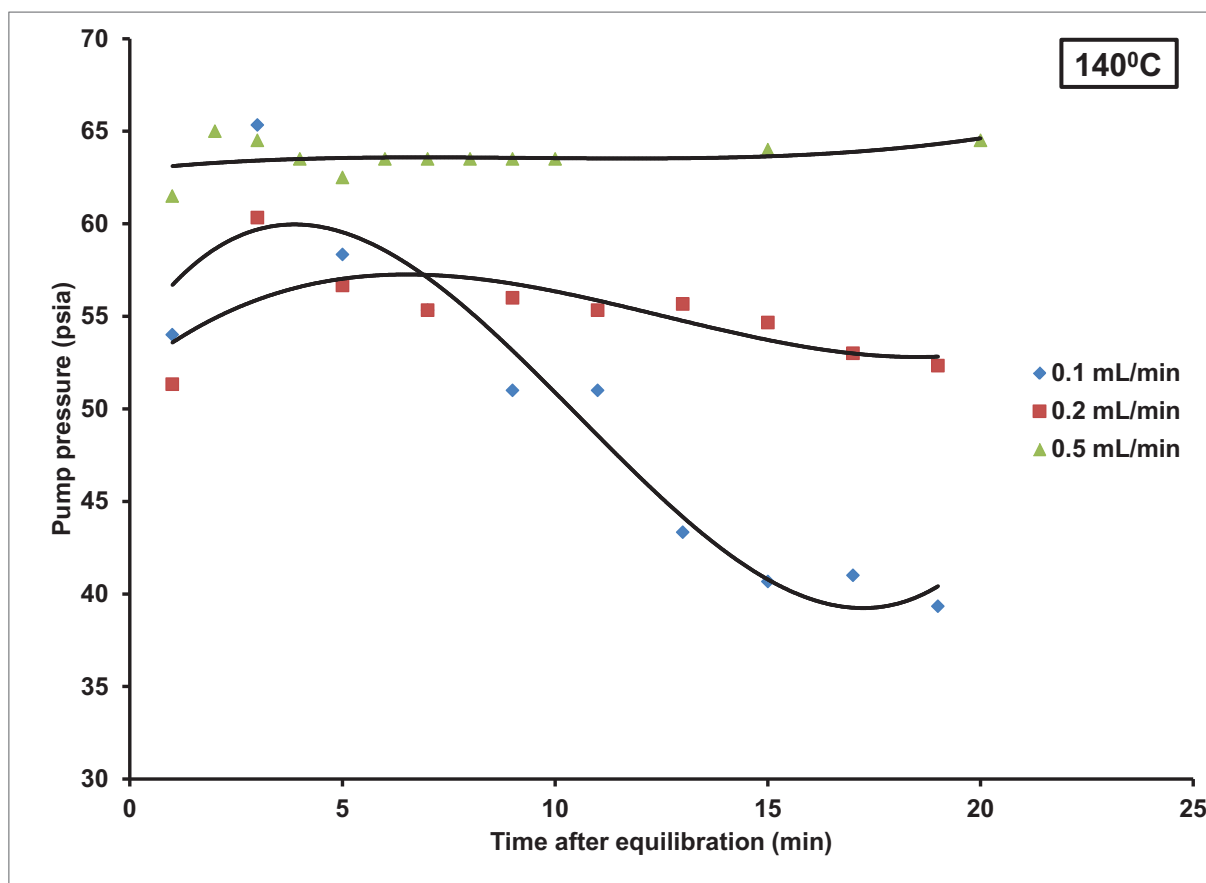


Figure 6: Variation of Teledyne ISCO 260D pump pressure during the determination of the aqueous solubility of quercetin dihydrate at 140°C with time at different solvent flow rates

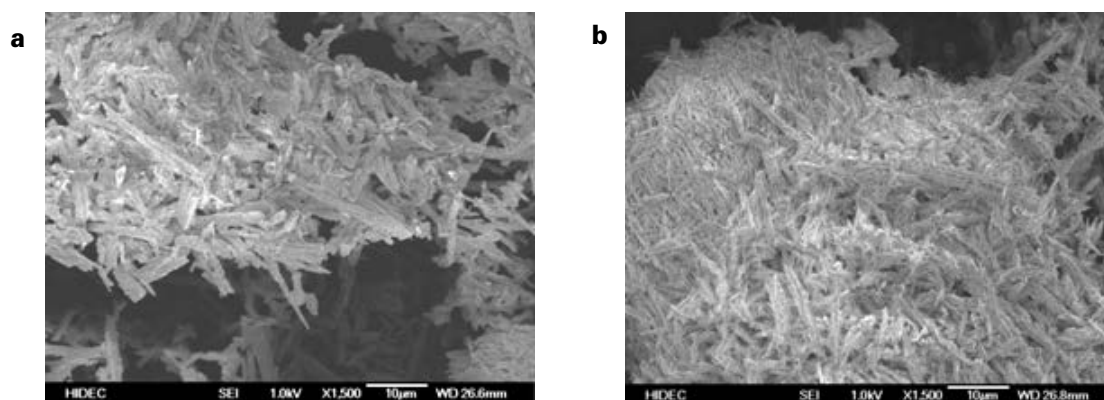


Figure 7: Scanning electron microscopy (SEM) images of (a) quercetin dihydrate at 250°C; and (b) quercetin dihydrate at 1400°C

References:

1. Cook, N. C. and Samman, S., 1996, Flavonoids-chemistry, metabolism, cardioprotective effects, and dietary sources, *J. Nutr. Biochem.*, 7, 66-76.
2. Yu, Y and Wu, H., 2010, Characteristics and Precipitation of Glucose Oligomers in the Fresh Liquid Products Obtained from Hydrolysis of Cellulose in Hot-Compressed Water, *Ind. Eng. Chem. Res.*, 48, 10682-10690.
3. Miller, D. J. and Hawthorne, S. B., 2000, Solubility of liquid organics of environmental interest in subcritical (hot/liquid) water from 298 K to 473 K, *J. Chem. Eng. Data.*, 45, 78-81.
4. Zhang, D., Montanes, F., Srinivas, K., Fornari, T., Ibanez, E. and King, J. W. 2010, Measurement and correlation of the solubility of carbohydrates in subcritical water, *Ind. Eng. Chem. Res.*, 49, 6691-6698.
5. Srinivas, K., King, J. W., Howard, L. R. and Monrad, J. K., 2010, Determination of solubility of quercetin and quercetin dihydrate in subcritical water using a dynamic flow technique, *J. Food Eng.*, 100, 208-218.
6. Srinivas, K., King, J. W., Howard, L. R. and Monrad, J. K., 2010, Solubility of gallic acid, catechin and protocatechuic acid in subcritical water from (298.75 to 415.85) K, *J. Chem. Eng. Data*, 55, 3101-3108.
7. Tomasink, P., *Advances in Carbohydrate Chemistry and Biochemistry- Vol. 47*, Academic Press Inc., New York, 1989, 203.
8. Noubigh, A., Cherif, M., Provost, E. and Abderrabba, M., 2008, Solubility of gallic acid, vanillin, syringic acid and protocatechuic acid in aqueous sulfate solutions from (298.15 to 318.15) K, *J. Chem. Eng. Data*, 53, 1675-1678.

Note:

The 260D model pump and the SFX 200 controller, which were used during the original experiment, are discontinued. The current model 260x pump and the SyriXus controller are the recommended replacements for the older 260D and SFX 200 models.

*October 31, 2012; revised November 7, 2023
Product model names have been updated in this document to reflect current pump offerings.*

Teledyne ISCO

P.O. Box 82531, Lincoln, Nebraska, 68501 USA
Toll-free: (800) 228-4373 • Phone: (402) 464-0231 • Fax: (402) 465-3091
www.teledyneisco.com

Teledyne ISCO is continually improving its products and reserves the right to change product specifications, replacement parts, schematics, and instructions without notice.

