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Dynamic and static characteristics of drug dissolution in supercritical CO2 by infrared spectroscopy: measurements of acetaminophen solubility in a wide range of state parameters.

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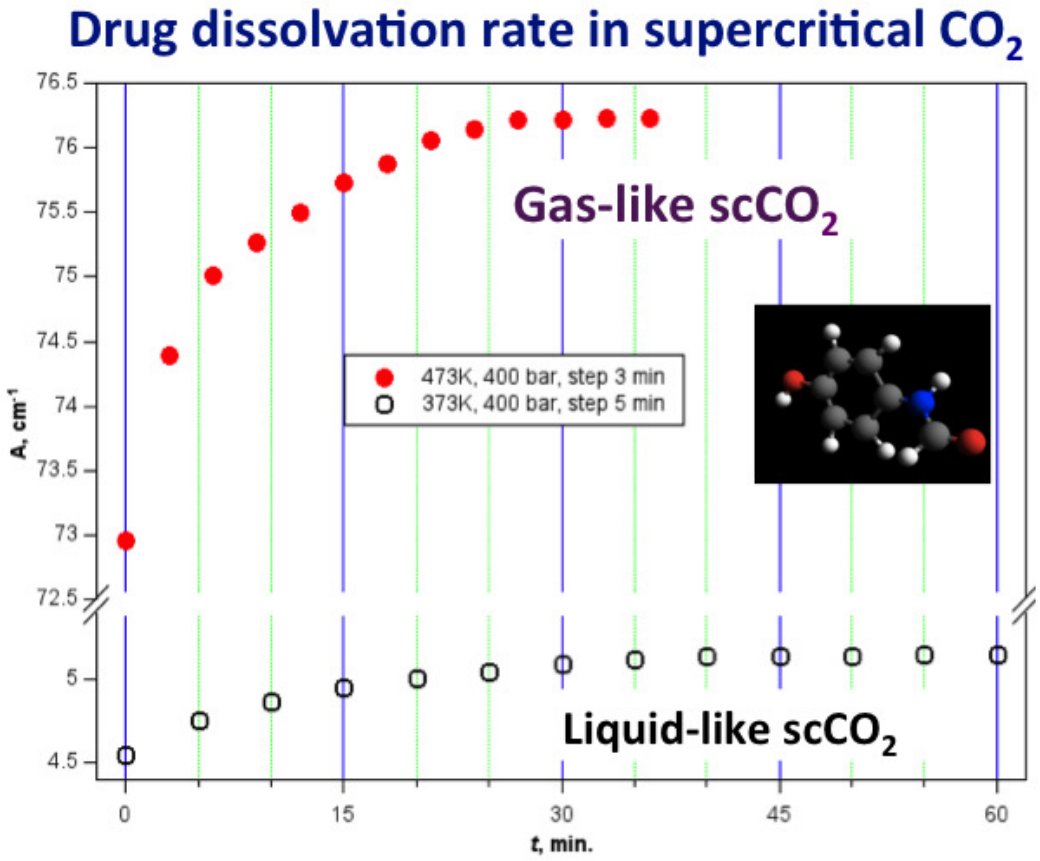
ABSTRACT. In this work we use vibration infrared spectroscopy to investigate solubility properties of bioactive substances in Supercritical CO_2 ($scCO_2$). By using acetaminophen as a model compound we show that the method can provide high sensitivity that makes it possible to study solubility at small concentrations, up to 10^{-6} $mol.l^{-1}$. This method also allows one to investigate kinetics of dissolution process in supercritical solvent. Our measurements at two different points of the (P,T) plane ((400 bar, 373K) and (400 bar, 473K)) have shown significant

difference in the kinetic mechanisms of acetaminophen dissolution at these two states: at higher temperature the dissolution process in $scCO_2$ has *two steps*: (i) 'fast' step when the acetaminophen concentration in $scCO_2$ quickly reaches 70-80% of the saturation level and (ii) a consequent 'slow' step where the acetaminophen concentration slowly increases up to the saturation level. However, at lower temperature, the dissolution process has only one, 'slow' step.

Keywords: supercritical solvents, $scCO_2$, infrared spectroscopy, bioactive molecules, mechanisms of solvation, solubility of drugs.



TOC figure

INTRODUCTION. During the last decade there has been a wave of interest in solvation properties of supercritical fluids (SCF). This wave has been stimulated by a large number of SCF applications in different areas ranging from pharmaceutics[1,2,3] and food industries[4,5] to molecular electronics.[6] Indeed, SCF solvents offer a significant increase in solubility for many compounds compared to their solubility under ambient conditions. Moreover, the solvent power of SCFs can be easily adjusted by varying pressure and/or temperature (for some compounds their solubility in SCFs can vary up to several orders of magnitude depending on the state parameters[25]). Therefore, depending on the state parameters *the same* SCF substance can act as solvent as well as anti-solvent for selected compounds.[7,8] This feature makes SCFs to be very suitable media for selective extraction, purification and precipitation as well as many other practical applications.

Supercritical carbon dioxide ($scCO_2$) has many attractive properties such as relatively low values of the critical pressure and temperature (P ~ 74 bar and T ~ 304 K), low toxicity, inflammability and low cost. As a consequence, $scCO_2$ and its mixtures with other compounds became the most widely used SCF solvents these days.[4,9] scCO2-based methods allow one an effective control of particle size and polymorphism[1,2,4] and in pharmaceutical industry the use of $scCO_2$ is a promising alternative to standard techniques for extraction, drying and crystallization that use environmentally hazardous solvents such as acetone, carbon tetrachloride, dimethyl sulfoxide, etc. Indeed, using scCO2 in pharmaceutical applications can help to solve at least two challenging problems: (i) expensive cleanup and ecologically-friendly utilization of solvents; (ii) eliminating the traces of solvents in the final product that might still remain there in a small, but still a dangerous concentration. In addition, $scCO_2$ can be used as anti-solvent to precipitate the formed crystalline phase.[10,11]

Although this is a rapidly developing field, there still remain many fundamental questions on physical-chemical mechanisms of solvation in $scCO_2$ to be understood. Such, there is an intriguing question on the dependency of the solvation mechanisms in an SCF on the state parameters. Indeed, there is a significant number of experimental and theoretical works that show that solvation mechanism in SCF solvents can be quite different for different parts of the (P,T) plane.[10,12,13,14,15,16,17,18,19,20,21,22]

However, there is a certain lack of studies on solubility of biologically active compounds in $scCO_2$ in a wide range of state parameters. Judging by the literature analysis of the subject, the most of published data report solubility values in quite narrow ranges of thermodynamic state parameters (presumably due to complications associated with experimental setup at high pressures and temperatures). Even less is known about *kinetics* of dissolution of drug compounds in $scCO_2$ because the most of currently used techniques for determining solubility in SCF solvents either use chromatography-based methods[23] that have limitations in terms of the accessible time resolution or use methods that cannot give the *quantitative* information about the concentration dependency with time as, e.g., the vanishing point method.[13]

In the present study we use the *vibration infrared spectroscopy* method to investigate solubility properties of bioactive substances in $scCO_2$. We show that with proper calibration it is possible to use this technique as an express-diagnostics method for determining solubility. We also show that the proposed method has high sensitivity that makes it possible to study the solubility at small concentrations, up to 10^{-6} $mol.l^{-1}$ in the present study. Moreover, this method allows one to investigate kinetics of dissolution process and, therefore, can give useful insights into physical-chemical mechanisms of solvation in SCFs.

EXPERIMENTAL SECTION

Figure 1 shows the experimental setup, which consists of a control system for pressure and temperature, high-temperature and high-pressure cell. To perform the IR experiments we used a high-pressure measurements cell, described in,[24] which has been specially upgraded for the presented work. This cell was made of a special alkali- and acid-resistant stainless steel and equipped with two cylindrical sapphire windows, spaced about 5 mm from each other (which define the thickness of the sample). The windows were mounted in special holders and sealed by round flexible graphite gaskets placed between the planes of the windows and the holder, as well as the plane of the clamping cap. The same sealing gaskets were placed between the holders of the windows and the body of the cell.

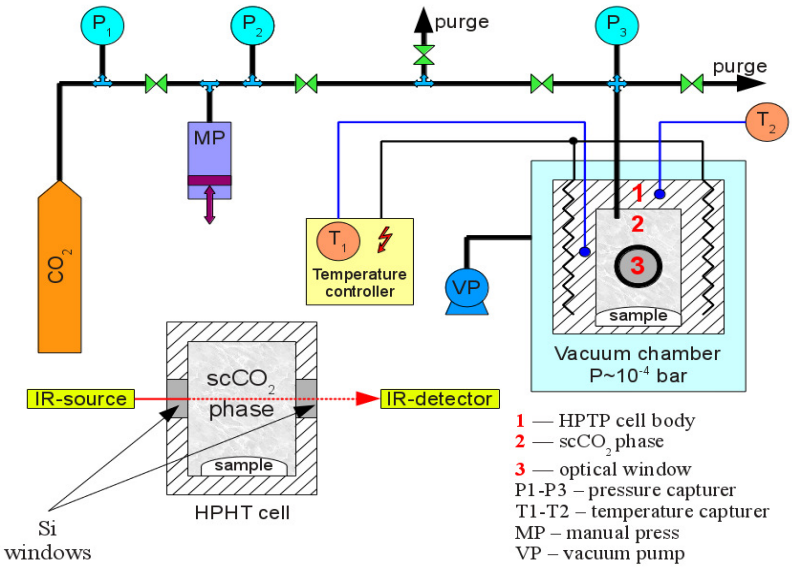


Figure 1. Scheme of the experimental setup used in this work.

To improve the quality of the spectra and reduce the influence of the atmospheric water vapor and carbon dioxide, we kept the working chamber of the spectrometer under vacuum during the

solubility experiments. We used a powerful vacuum pump that allowed us to decrease quickly the chamber pressure to ~ 10^{-4} bar.

To heat the cell placed in the working chamber of the spectrometer we used four cartridge heaters located at the corners of the cell. To control the heat, we used two submersible contact thermocouples, one was placed in a close neighborhood of the heating element; another one was placed in the sample zone to control the temperature gradient. We varied the pressure in the cell by injection of carbon dioxide entering the capillary from the hand press pump coupled with a balloon. This equipment allowed us to control the temperature of the sample in a wide range of state parameters with an accuracy of ± 0.5 K, and the use of a specially designed hand-press allows us to keep the pressure up to 2 kbar, with an accuracy of ± 0.1 bar.

We used samples of acetaminophen with 98%purity bought from Sigma-Aldrich. Before the solubility measurements the samples were pre-dried under vacuum conditions. The samples were placed at the bottom of the cell (see Figure 1). With increasing the temperature and pressure, the concentration of acetaminophen in the $scCO_2$ phase (see Figure 1) increased, reaching the thermodynamic equilibrium in a relatively short period of time. We obtained the IR spectra of the studied samples by a Fourier-transform spectrometer Bruker VERTEX 80v. For each measurement we collected 128 interferograms which then were averaged out to decrease the statistical noise. The spectra were recorded in the spectral range 1000-6000 cm^{-1} with a resolution of 1 cm^{-1}. The background spectrum was recoded with empty vacuum chamber. The spectra of neat CO_2 and CO_2+Acetaminophen were recorded under the same thermodynamic state parameters. In turn the resulting absorption spectra of acetaminophen dissolved in $scCO_2$ phase were calculated by subtracting the spectra of CO_2 from spectra of CO_2+Acetaminophen.

In order to calculate the concentration of components in the solute-solvent system from the IR spectral profile of a given vibration mode, we use the Bouguer-Lambert-Beer law $I = l \cdot \varepsilon \cdot c$, where l is the thickness of the sample; ε is the molar absorption coefficient (extinction coefficient) that does not depend on the thickness of the absorbing layer and the intensity of the incident light, c is the concentration of the material and I is the *optical* density.

RESULTS and DISCUSSIONS. We have applied this method to investigate the solubility of acetaminophen in $scCO_2$ in a wide range of parameters: from the low-density SCF state (P=75 bar, T=348 K) to the high-density SCF state (P=400 bar, T=473 K). We also investigated time-dependence of the acetaminophen dissolution process in different parts of the (P,T) diagram selecting two characteristic points (P=400 bar, T=373 K) and (P=400 bar, T=473 K).

To determine the concentration of a component in the solute-solvent system it is necessary to calculate the molar absorption coefficient associated with its characteristic spectral band. In turn, the selected spectral band(s) should not overlap with the spectral contribution of the other components (solvent or/and co-solutes). In the case of a binary system acetaminophen + carbon dioxide, we selected the spectral band of acetaminophen around 1507-1513 cm^{-1} that corresponds to the symmetric bending vibrations of the CH group in the benzene ring.[25] As it shown in figure 2, where the spectra of $scCO_2$ + cell and $scCO_2$ + cell + acetaminophen at 473 K in the pressure range of 75-400 bar are depicted the neat $scCO_2$ spectra indicate that over the entire range of pressures, the spectral region 1450-1600 cm^{-1} is free from any contribution of $scCO_2$. However, in the case of a binary system acetaminophen-$scCO_2$ in this spectral region there is a spectral contribution at ν =1513 cm^{-1} (the peak appears at P = 75 bar). The intensity of this peak rapidly increases with increasing pressure. Consequently, this band is associated with

the presence of acetaminophen in the $scCO_2$ phase (see Figure 3). Therefore, this band was chosen for the calculation of dissolved acetaminophen concentration in $scCO_2$ solvent.

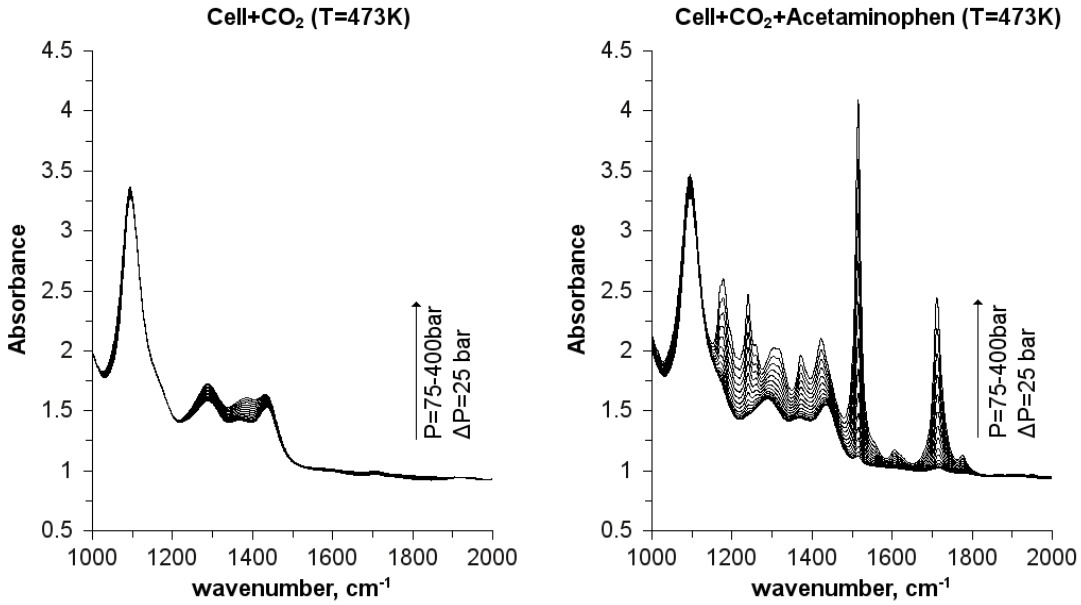


Figure 2. IR spectra of experimental cell containing $scCO_2$ (left) and solutions of acetomenaphen in $scCO_2$ (right) along isotherm of 473 K in the pressure range of 75-400 bar with an increase step of pressure ΔP=25 bar.

Furthermore, using the maximum of optical density *I* to determine the concentration of the dissolved species often leads to errors associated with the contribution of more than one spectral contribution as well as with their associated dispersions. Therefore in this paper we will use the integral intensity *A* and integrated molar absorption coefficient ε_I of the chosen vibration mode.

Figure 3 represents the difference between the spectra of the binary system acetaminophen+$scCO_2$ and the spectra of pure $scCO_2$. The presented data show that at T = 348 K and a pressure of P= 75 bar the band intensity at ν = 1507-1513 cm^{-1} is comparable with the noise level and, consequently, this band can not be identified. However, this band is clearly identified at P=150 bar. Furthermore, when the temperature is increased, this band is well

resolved at even low pressure. Thus, at T=373 K, the peak appears already at P = 125 bar, and in the temperature range 398-473 K it is well visible in the whole range of investigated pressures.

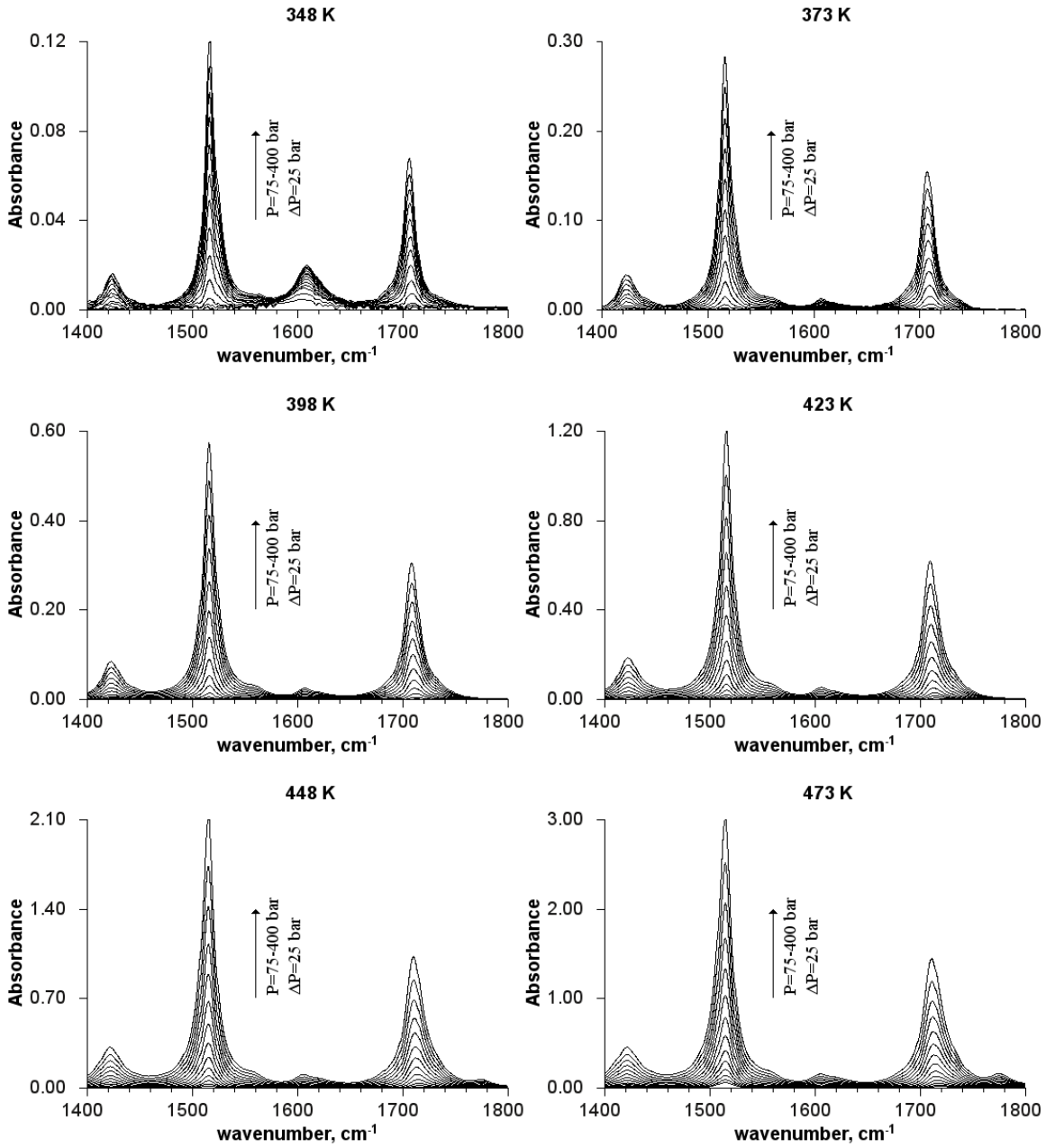


Figure 3. IR spectra of acetaminophen dissolved in the $scCO_2$ phase along 348K, 373K, 398K, 423K, 448K, 473K isotherms in range of pressures 75-400 bar. These spectra were obtained by subtracting the spectra contribution of $scCO_2$ recorded at the same state parameters.

According to the literature data,[25] solubility of acetaminophen in supercritical carbon dioxide has low values ranging from 10^{-8} mole fraction at T=353 K and P=80 bar to 10^{-6} mole fraction at T = 353 K and P = 250 bar. Moreover, equilibrating the concentration of acetaminophen in the $scCO_2$ phase can take a while[7,8,9,10] (the equilibration time strongly depends on the temperature and various kinds of extra external physical factors such as, for example, ultrasonification, shaking etc;[7,8,9,10,11,12] see also discussion below). However, in the case of a sealed system such as the optical IR-cell used in this work, application of external mechanical stresses on the system to speed up the process of dissolution is fairly complicated. Therefore, in our experiments the only driving force of the dissolution process is diffusion through the concentration gradient and this allows us to analyze the kinetic of dissolution of acetaminophen.

The advantage of the spectroscopic method used in this work is that it allows to follow in situ the kinetic of dissolution by measuring the time dependence of *A(t)* which is proportional to the concentration of the dissolved acetaminophen in $scCO_2$ phase.

The value of the integrated intensity *A(t)* at a given time *t,* can be obtained by decomposition analysis of the experimental IR spectrum. In the presented study, the peak decomposition for the part of the spectrum that corresponds to the symmetric deformation fluctuations of the C-H group in the benzene ring of acetaminophen is quite straightforward. Actually, this peak can be already well approximated by only one Lorentzian profile. However, to improve the accuracy of solubility calculations, somewhat more accurate approximation of the peak is required; that was done by introduction of additional Gaussians for approximation of the satellite peaks on the spectrum located in the high and low frequency sides of the chosen peak. Approximation and decomposition of experimental spectra was done with use of a software package for spectroscopic analysis "Fityk".[26]

To estimate the time dependence of *A(t)* we recorded every 5 min the IR spectrum at 373 K and 473 K and a pressure of 400 bar. The measurements have been carried out as long as the integrated intensity *A(t)* of the peak at ν=1513 cm^{-1} didn't reach a plateau indicating the maximum value A_{max} and then the maximum of solubility. Figure 4 shows the time dependences *A(t)* of the spectral band ν =1513 cm^{-1} at P = 400 bar and at two different temperatures, T = 373 K and 473 K. In order to quantify the rate of change of the absorbance, we carried out a fitting procedure. The time evolution of *A(t)* is well represented by an exponential law that can be described by the following equation:

$$A(t) = A_{max} - B_1 \cdot \exp(-t/\tau_1) - B_2 \cdot \exp(-t/\tau_2) \quad (1)$$

A_{max} is the integral intensity of the saturated solutions; B_1 and B_2 are constant, τ_1 *and* τ_2— characterize the rate of increase of *A(t)*.

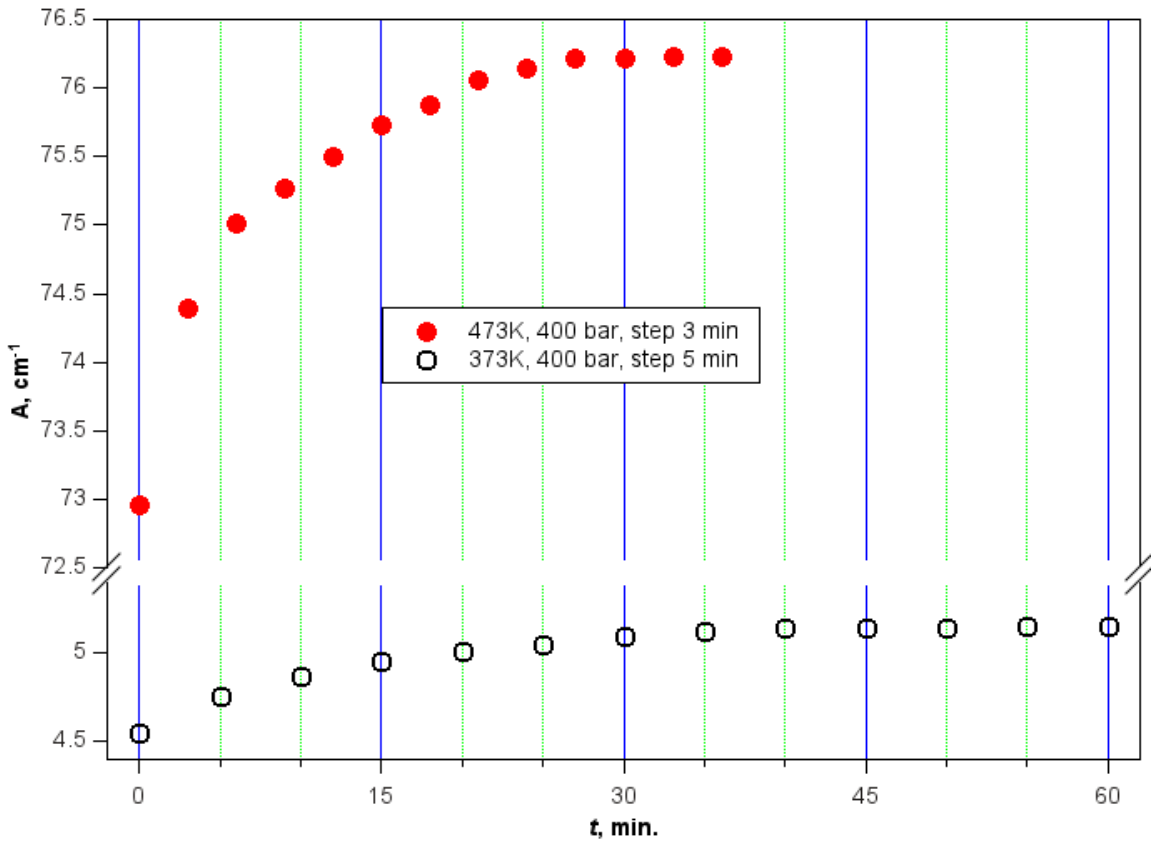


Figure 4. Acetaminophen dissolution in the $scCO_2$ phase with time at two different temperatures, T = 373 K (black empty circles) and 473 K (red filled circles); pressure was kept the same in both experiments at P = 400 bar. The figure shows time dependences of the integral intensity *A* of the spectral band ν =1513 cm^{-1}.

According to the results of the approximation of the *A(t)* dependencies by the equation (1) for the case of T=473 K the values τ_1 *and* τ_2 have values of 1.44 min and 11.15 min, respectively. Therefore, the time dependence of the integral intensity in this case can be described by two different processes (i) 'fast' step characterized by τ_1 when the acetaminophen concentration quickly reaches a level of up to 70-80% from the saturation and (ii) a consequent 'slow' step characterized by τ_2 where the concentration slowly increases up to the saturation level. However, we note that at T = 373 K the same analysis of *A(t)* dependence reveals only *one* significant rate

constant, τ=13.82 min that corresponds to domination of slow dissolution process at this temperature (see also discussion below).

Furthermore, the time requited to reach the plateau of maximum solubility was estimated from these data to be between 30 (high temperatures) and 60 min (low temperatures).

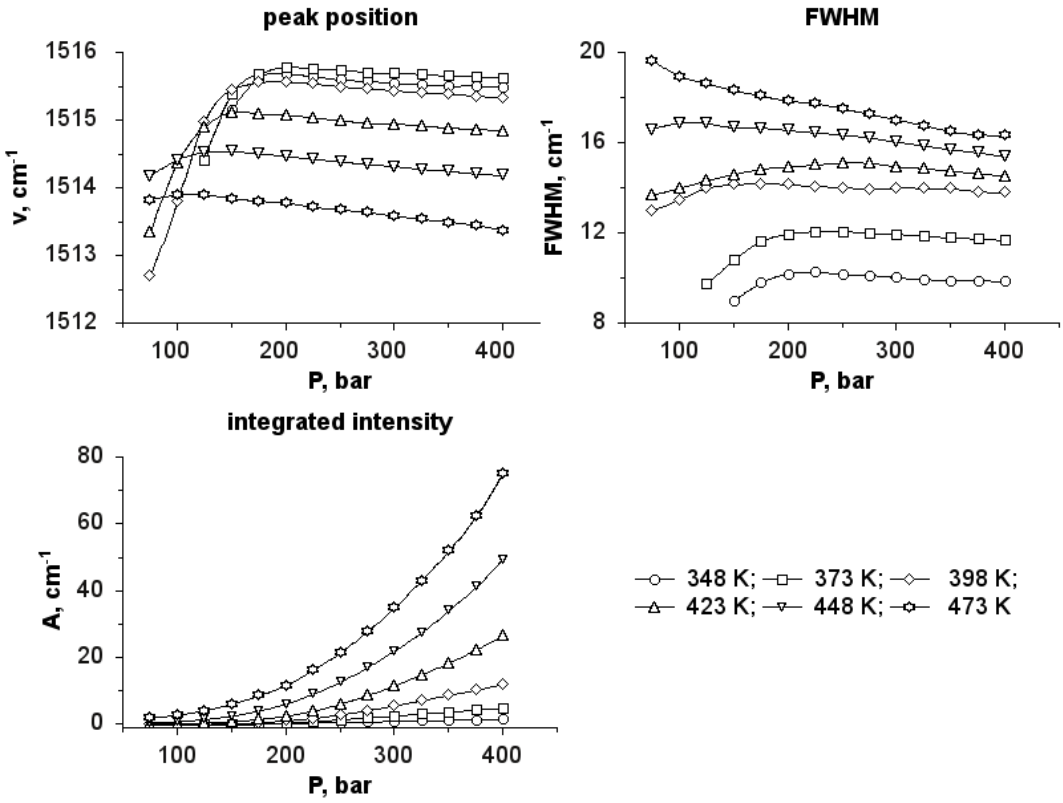


Figure 5. The pressure and temperature dependence of the peak position, the FWHM and the integral intensity of acetaminophen C-H vibration mode.

To get more insights on the dependence of acetaminophene solubility from state parameters we studied the pressure and temperature dependence of the dissolution of acetaminophen at various isotherms T=348 K, T=373K, T=398K, T=423K, T=448K, T=473K. After carrying out a fitting procedure on the CH deformation spectral profile, we show in Figure 5 the pressure and

temperature dependence of the position of the CH symmetric deformation of the benzene ring, of its full width at half maximum (FWHM), and of the integrated intensity A.

These results demonstrate that there is an overall small shift (less than 3 cm^{-1}) of the wavenumber of the CH symmetric deformation of the benzene ring when the pressure is changed along the studied isotherms. Interestingly, for isotherms lower then $T_{m.p}$ ($T_{m.p}$ =442-445 K) increasing the pressure induces a shift to higher frequencies. Furthermore, for lower isotherms than $T_{m.p}$, increasing the pressure below 200 bar induces, an increase of the FWHM and these values remain constant for further increase of the pressure. However for isotherms higher than $T_{m.p}$, increasing the pressure induces a decrease of FWHM values. This behavior suggests that changing the temperature or pressure favors one of the various conformations of acetaminophen; more detailed study of this effect will be a subject of our future works.

Interestingly, the results show that increasing the pressure induces an increase of A (and, consequently, the solubility), particularly at temperatures higher than the melting point of acetaminophen ($T_{m.p}$=442-445K).

In order to determine the acetaminophen solubility we need to know the integrated molar absorption coefficient ε_I. To determine this parameter we applied the following procedure: first we used the values of solubility of acetaminophen in $scCO_2$ obtained by Brisow et al.[27] Indeed, in this study the solubility (in unit of mole fraction) of acetaminophen was estimated in the range of pressure between 80 and 300 bar for two isotherms 313 K and 353 K. We calculated the integrated molar absorption coefficient for pressure values of 150, 200 and 250 bar along the isotherm T=353K. The results are summarized in table 1. As one can see from this table, the integrated extinction coefficient practically does not change with the pressure as its values vary only within 0.3% deviation from the average value of $\langle\varepsilon_I\rangle = 7.01 \cdot 10^3\ mol^{-1}.\ l.\ cm^{-2}$.

Table 1. The integrated molar absorption coefficient (ε_I) as calculated from eq. 2 using reference data of acetaminophen concentrations at T=353K and selected pressures taken from Ref.[25]

P, bar	c, mol.l^{-1}	ε_I ($mol^{-1}.\ l.\ cm^{-2}$)
150	$1.32\cdot10^{-5}$	$7.01\cdot10^{3}$
200	$5.90\cdot10^{-5}$	$7.03\cdot10^{3}$
250	$1.27\cdot10^{-4}$	$6.99\cdot10^{3}$

These results show that the integrated molar absorption coefficient ε_I does not significantly vary with the change of pressure. We then assume that this value remains constant for the range of state parameters used in our study. This allows us to estimate the molar concentration of acetaminophen, $c_{Ac,}$ in the system using the average value of $<\varepsilon_I>$ calculated above as:

$$c_{Ac} = A / <\varepsilon_I> . \tag{3}$$

Therefore, we can calculate the molar fraction of acetaminophen, x_{Ac} in scCO$_2$ as:

$$x_{Ac} = c_{Ac} / (c_{Ac} + c_{CO_2}), \tag{4}$$

where c_{CO_2} is the molar concentration of scCO$_2$. Because $c_{Ac} << c_{CO_2}$, the relation (4) can be simplified as $x_{Ac} = c_{Ac} / c_{CO_2}$, and, consequently, using (3), we obtain: $x_{Ac} = A/(<\varepsilon_I>\cdot c_{CO_2})$.

Here we calculate c_{CO_2} by the equation of state given in.[28]

Figure 6 illustrates the behavior of the molar fraction of acetaminophen as a function of both the pressure and temperature, $x_{Ac}=f(T,P)$. (Numerical values of measured solubilities are given in the supplementary materials to this paper).

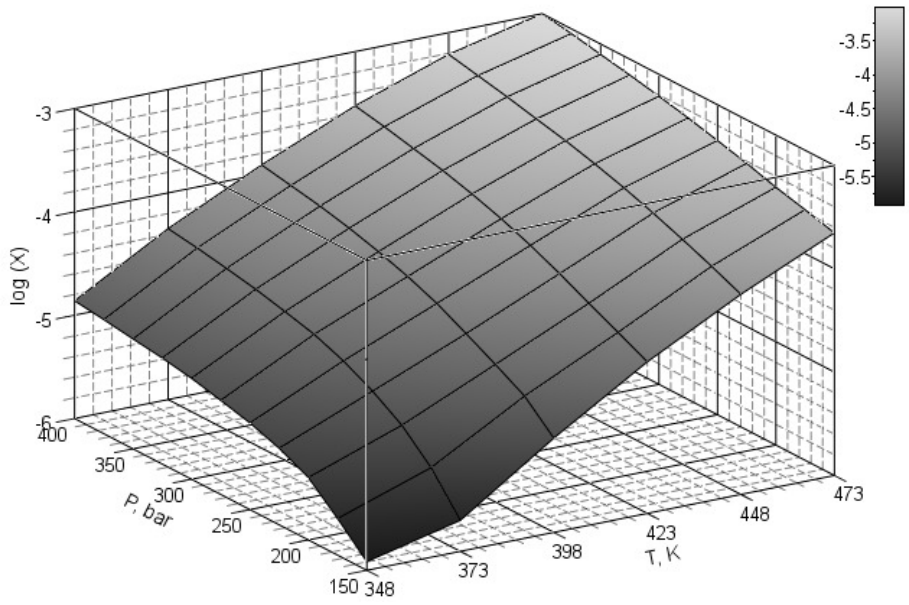


Figure 6. Solubility of acetaminophen as a function of pressure and temperature.

The presented results on this figure show that increasing the pressure at high temperature induces a large increase in the acetaminophen solubility. Thus, the solubility of acetaminophen changes in two orders of magnitude (from $1.24\cdot10^{-6}$ to $9.48\cdot10^{-4}$ $mol.l^{-1}$) from the point of (P=150 bar; T=348 K) to the point of (P=400 bar, T=473 K). However, the temperature has more influence on the solubility of acetaminophen in $scCO_2$ than pressure. We note, however, that there is not clear visible crossover 'ridge' on this plane.

To summarize: in this work we present an IR spectroscopy-based method for determining solubility of drug compounds in $scCO_2$. The method has an advantage of being fast and non-

invasive; the method can also be used for studying dynamics of the dissolution process in $scCO_2$-based solvents. That allowed us to investigate solubility of acetaminophen in a wide range of (P,T) parameters and obtain results for high pressures and temperatures (up to 400 bar and 473 K) that are not easily accessible by standard chromatographic methods.[21]

We also investigated dynamics of the dissolution process in the two distinct parts of the (P,T) diagram, at the point of (P=400, T=373K) that (as we estimate) is below the dynamic crossover (Frenkel line[20]) for $scCO_2$ and at the point of (P=400, T=473K) that (as we estimate) is along the Frenkel line for $scCO_2$ (see the supplementary materials, figure S1). According to the general conclusions from Ref.[19] the first point corresponds to a liquid-like state of $scCO_2$ and the second point corresponds to a gas-like state of $scCO_2$. The results show a significant difference in the kinetic mechanisms of dissolution of acetaminophen in these two states of $scCO_2$; in the gas-like state the dissolution process has *two steps*: (i) 'fast' step when the acetaminophen concentration quickly reaches a level of up to 70-80% from the saturation and (ii) a consequent 'slow' step where the concentration slowly increases up to the saturation level. However, in a liquid-like $scCO_2$ state, the dissolution process has only, one, 'slow' step.

These results form a basis for future investigations of the solubility behavior in different points on the (P,T) diagram. Indeed, in several works there has been shown that there is a crossover between the high-density SCF and low-density SCF.[29,30] Such, Nishikawa and Tanaka measured small-angle X-ray scattering intensities for several (P, T) states of supercritical $scCO_2$;[31] they observed that measured correlation lengths and density fluctuations take maximum values along the extension of the gas/liquid coexistence curve to the supercritical region (see also[32,33]). We note that this crossover is often attributed to the so-called Widom line that is "thermodynamic" continuation of the boiling curve, the line of the maxima of thermodynamic properties in the

vicinity of the critical point.[19,20] However, there are still debates in the literature whether this crossover is indeed related with the Widom line. (The position at phase diagrams of experimental data, where kinetics have been measured, compared to Widom line is given in figure S2 of supplementary materials). Such, Brazhkin et al argued in their recent work[20] that the crossover should correspond to "the disappearance of high-frequency sound" and "qualitative changes in the temperature dependencies of sound velocity, diffusion, viscous flow, and thermal conductivity, an increase in particle thermal speed to half the speed of sound, and a reduction in the constant volume specific heat to $2k_B$ per particle." They called the new dynamic line as Frenkel line (see Ref.[20]).

The method proposed in the presented work can be used for detailed screening of the solubility behavior in different parts of the (P,T) plane and it would be interesting to see whether the general conclusions from these fundamental works on non-linear dependence of solubility in an SCF solvent from the (P,T) state parameters can be reproduced on a system of practical relevance, such as, e.g. pharmaceutics in $scCO_2$. This is the subject of our ongoing investigation.

We note that for determining absolute values of the solubility the proposed method requires a calibration using results obtained by other methods, e.g. chromatography. That may sound as a drawback. However, we note that, once calibrated on a few external data points, the method can be used for determining a large amount of solubility values in a wide area of (P,T) parameters (provided that the spectroscopic cell remains the same). That can be very helpful for optimizing parameters of a $scCO_2$-based solvent required for a particular application (e.g. extraction or micro-particle formation etc). Due to its non-invasive nature, the method can be also used for express diagnostics of dissolution processes in various applications of $scCO_2$ solvents. We note

that this is a pilot study and in our future works we will apply method for studying effects of additives in $scCO_2$ on static and dynamic solvation parameters of bioactive molecules.

ASSOCIATED CONTENT

Supporting Information

Estimated positions of Frenkel and Widom lines for $scCO_2$. Table of numerical values of measured solubilitilies of acetaminophene in $scCO_2$ for the whole range of temperatures and pressures used in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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