Solubility of Nifedipine and Nitrendipine in Supercritical CO_2

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The solubilities of nifedipine and nitrendipine in supercritical CO_2 were measured by a static–analytical method in the pressure range from 100 to 300 bar at temperatures of 60, 80, and 100 °C. The mole fraction solubility of nifedipine at 300 bar and 100 °C is 7.1×10^{-5}, and that for nitrendipine is 10.6×10^{-5}. The difference in the solubilities of both compounds is small due to the similar chemical structure and physical properties. The applicability and limitations of three density-based models used to correlate the results are discussed.

1. Introduction

High-pressure technologies offer the industry an enormous opportunity to develop products of high value, with completely new or improved properties. Sub- and supercritical fluid (SCF) extraction is a separation process that has received considerable attention over the last few years. Recently supercritical fluids have been applied as solvents for non extractive applications in high-pressure micronization and in chromatography and as chemical and biochemical reaction media. The advantages of using supercritical fluids to perform and achieve separations are well documented in several reviews (Paulaitis et al., 1982; McHugh, 1986; Brunner, 1990; Bruno, 1991; Kiran-Brennecke, 1993).

For the design of a process in which SCF's are utilized, data are required for the pressure and temperature of the recovery stage, the type and quantity of the solvent, the recirculation rate, and energy consumption. This information can be obtained from phase equilibria, mass transfer measurements, and the thermodynamic analysis of the process.

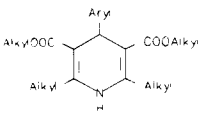
Modeling the solubility of solids and liquids in supercritical fluids, using density instead of pressure as the independent variable, does not require the aforementioned physical properties and in this respect is very interesting (Knez-Steiner, 1992). There exist several empirical density-based correlations (Johnston-Eckert, 1981; Chrastil, 1982; Schmitt-Reid, 1985; Kumar-Johnston, 1988). The solubilities of nifedipine and nitrendipine in supercritical CO_2 were determined due to our research work on the particle formation PGSS (particles from gas-saturated solutions) (Weidner et al., 1994). Data were correlated with three density-based models.

2. Calcium Antagonists (van Zwieten et al., 1983; Reid et al., 1988)

Calcium antagonists or calcium entry blockers are a biochemically heterogeneous group of cardiovascular drugs that share the property of blocking the entry of calcium ions into cells by voltage-operated channels in cardiac and smooth muscle.

Calcium entry blockers comprise a various range of chemical structures. One class of compounds are dihydropyridines, derivatives of the general structure dialkyl 4-aryl-1,4-dihydropyridine-3,5-dicarboxylates (Figure 1a).

For our studies, we have chosen two derivatives of 1,4-dihydropyridine, nifedipine and nitrendipine. These are



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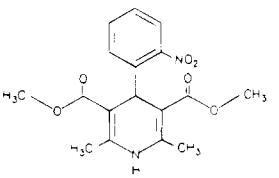

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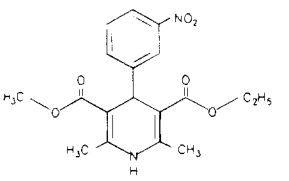

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Figure 1. Chemical structures of dialkyl 4-aryl-1,4-dihydropyridine-3,5-dicarboxylates (a), nifedipine (b), and nitrendipine (c).

poorly water-soluble compounds (the solubility of nifedipine being about 11 mg/L of water at 37 °C). They possess low chemical stability. Nifedipine is very sensitive to light and also to air and undergoes degradation, when exposed to air and daylight.

Nifedipine is chemically dimethyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate (Figure 1b) and nitrendipine is methyl ethyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate (Figure 1c).

3. Experimental Section

3.1. Apparatus and Experimental Procedure. For the measurements of the solubility of substances in supercritical CO_2 a static–analytical method was used. The basic scheme of the equipment is presented in Figure 2. The detailed description can be found in our previous paper (Knez-Steiner, 1992).

The equilibrium cell was fixed on a frame. By shaking the frame by means of a motor via an excenter, the solid and CO_2 phase were mixed and equilibrium was established. After 1 h phase equilibrium was reached and the frame was brought into a vertical position. After 1 h (time for sedimentation of solid particles) a sample of nifedipine– or nitrendipine–supercritical CO_2 solution was taken by the use of a sampling valve in a trap with ethanol. The concentration of the substance in ethanol was determined by UV spectrometry. The accuracy of the method was

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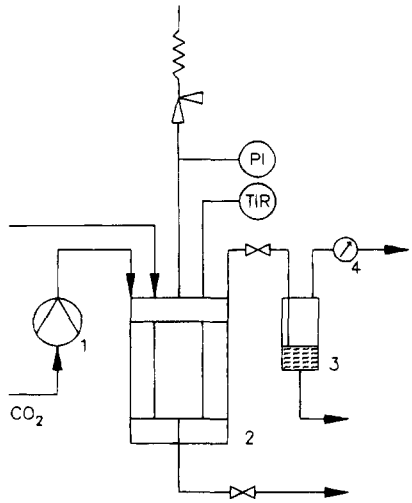

Figure 2. Flow diagram of the experimental equipment: (1) high-pressure pump, (2) autoclave with external heating, (3) sampling trap, (4) rotameter.

±0.5%. Since the quantity of the sample was sufficiently small compared to the volume of the equilibrium cell, further experiments could have been done after a particular time lapse needed to obtain equilibrium. The temperature of the high-pressure equilibrium cell was controlled within ±0.5 °C, and the pressure was measured by using a Digibar gauge, Hotinger Baldwin Messtechnik (accuracy ±0.1%).

3.2. Materials. Nifedipine (purity 99.6%) and nitrendipine (purity 99.8%) were obtained from LEK pharmaceutical works, Ljubljana, Slovenia. Carbon dioxide was 99.99% (by volume) pure and supplied by LINDE plin, Celje, Slovenia. Ethanol, pro analysi (purity 99.8%), was from Merck, Darmstadt, Germany.

4. Data Correlation

Three methods for correlating the experimental equilibrium solubility data were examined.

A thermodynamic formalism was developed to correlate the solubility of a nonvolatile solute in a supercritical fluid as a function of the density of the fluid phase (Kumar-Johnston, 1988).

In general, the solubility of a solid component i in the gas phase, as a function of operating pressure and temperature, can be described as

$$y_i = \frac{P_i^{sat}}{P\Phi_i} \exp\left[\frac{v_i^s(P - P_i^{sat})}{RT}\right] \tag{1}$$

where

$$\ln \Phi_i = \int_0^P \left(\frac{\bar{v}_i}{RT} - \frac{1}{P}\right) dP \tag{2}$$

y_i is the equilibrium mole fraction of the solute in the supercritical fluid phase, and P_i^{sat} is the saturated vapor pressure. v_i^s is the molar volume of the solid solute, R is the universal gas constant, P and T are the operating pressure and temperature, Φ_i represents the fugacity coefficient, and $\bar{v}_i$ is the partial molar volume of the solute. In addition, it has been assumed that the solute phase in equilibrium with the supercritical phase is pure and incompressible. The dependence of solubility on density cannot be readily seen from eq 1. Therefore, an alternative approach was developed (Kumar-Johnston, 1988) to express the fugacity coefficient of the solute, ψ_i, in terms of the density of the supercritical solvent instead of the pressure, as is done in the conventional thermodynamic treatment (eq 2). The function ψ_i can be obtained from an equation of state using the expression

$$\psi_i = \Phi_i Z \tag{3}$$

where Z is compressibility factor

$$Z = P/\varrho RT \tag{3a}$$

and therefore

$$\ln \psi_i = -\int_0^P \left(1 - \frac{\bar{v}_i}{RTk_T}\right)(d\varrho)/\varrho \tag{4}$$

where k_T is equal to $(1/\varrho)(\delta\varrho/\delta P)_T$ and is the isothermal compressibility of the fluid phase and ϱ is density. Hence, the formal expression relating the solubility of a crystalline solute in a supercritical fluid as a function of solvent density is

$$y_i = \frac{P_i^{sat}}{\varrho RT\psi_i} \exp\frac{v_i^s(P - P_i^{sat})}{RT} \tag{5}$$

The quantity $\bar{v}_i/k_T$ (which could be density dependent or density independent—depending on the system) determines whether either the plot ln y against ln ϱ_r or the plot ln y against ϱ_r forms a linear relationship, where ϱ_r is reduced density.

The following expressions describe the two possible (ln y)–ϱ_r relationships:

$$\ln y_i = C - \left(\frac{\bar{v}_i}{RTk_T}\right)_{\varrho_r=1} \ln \varrho_r \tag{6}$$

$$\ln y_i = C_1 - \left(\frac{\bar{v}_i}{RTk_T}\right)_{\varrho_r=1} \varrho_r \tag{7}$$

where C and C_1 are constants and θ is the slope of the ln y against ln ϱ_r or ln y against ϱ_r plot.

The model proposed by Chrastil (Chrastil, 1982) relates the solubility of a solute to the density of the supercritical solvent on the basis of the assumption that the molecule of a solute (A) associates with the k molecules of gas (C) with the formation of a solvato complex (AC), which is in equilibrium with the gas. The Chrastil equation can be written as

$$\log c = k \log \varrho + a/T + b \tag{8}$$

c is the concentration of a solute in a gas, ϱ is the density of the gas, and k is an association number and represents the slope of a plot of log c as a function of log ϱ at constant temperature.

Log c is a linear function of $1/T$ at constant density, and the constant a is the slope of that plot. The value of the constant b can be chosen to minimize the deviation of the model from experimental data. This correlation properly predicts that the solubility increases with increasing density (or pressure) at constant temperature rises at constant pressure.

5. Results and Discussion

Some physicochemical properties of nifedipine and nitrendipine are presented in Table 1.

The solubility results were determined at temperatures of 60, 80, and 100 °C and in the pressure range from 100 to 300 bar. The equilibrium mole fraction y_i of the solute in the supercritical CO_2 as a function of system pressure is presented in Figure 3 and in Table 2. The reproducibility

Table 1. Physical Properties of Nifedipine and Nitrendipine

compound	M_w/ (g/mol)	T_m/K	T_b[a]/K	T_c[b]/K	P_c[a]/ bar	V_c[a]/ (cm^3/mol)
nifedipine	346.34	444–448	691.6	873.4	17.8	935.5
nitrendipine	360.46	430–431	702.3	880.5	16.7	990.5

[a] Lydersen (1955). [b] Fedors (1982).

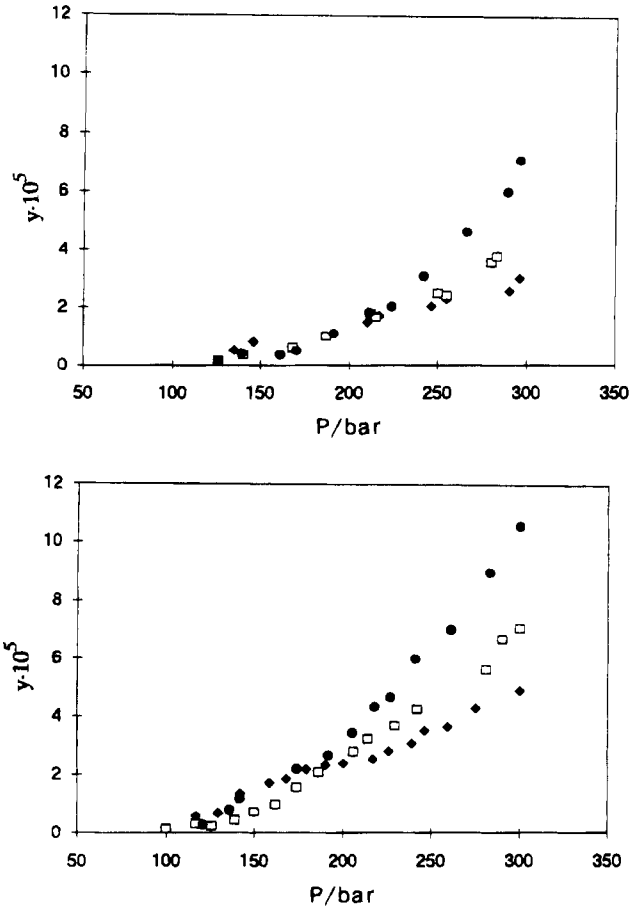

Figure 3. Solubility isotherms of (a, top) nifedipine and (b, bottom) nitrendipine as a function of pressure: (♦) 60 °C, (□) 80 °C, (●) 100 °C.

of the solubilities is within ±4.3% for nifedipine in the pressure range 100–300 bar, and for nitrendipine it is ±3.2%.

The effect of pressure on the solute solubility shows the usual trends. As the pressure is raised, the carbon dioxide density increases and the mean intermolecular distance of the carbon dioxide molecules decreases, thereby increasing the specific interaction between the solute and solvent molecules.

The second factor affecting the equilibrium solubility of a solid substance is the temperature of the system. The temperature influences the solute vapor pressure, the solvent density, and the intermolecular interactions in the fluid phase. At pressures under the crossover region (for nifedipine 220 bar and for nitrendipine 200 bar), the solvent densities are lowered by small increases in temperature; as the density effect is dominant in this region, the solubility will decrease with the raising of the temperature. At higher pressures, the solvent density is less dependent on temperature so the increase in solubility is primarily due to the higher vapor pressure of the solid.

The logarithm of the solubility of nifedipine and nitrendipine in supercritical CO_2 is a linear function of the logarithm of solvent density, as is shown in Figure 4. The increase in the solubility of nifedipine and nitrendipine

Table 2. Solubility of Nifedipine and Nitrendipine in Supercritical CO_2

60 °C			80 °C			100 °C		
P/bar	ϱ_{CO_2}/ (kg/m^3)	$10^5\,y$	P/bar	ϱ_{CO_2}/ (kg/m^3)	$10^5\,y$	P/bar	ϱ_{CO_2}/ (kg/m^3)	$10^5\,y$
				Nifedipine				
135.0	559.8	0.508	126.0	268.9	0.135	126.0	258.9	0.143
146.0	635.9	0.808	140.0	322.8	0.355	139.5	298.1	0.379
210.0	733.9	1.506	168.0	443.7	0.611	161.0	363.8	0.349
217.0	748.1	1.761	186.5	558.8	1.014	170.0	395.8	0.490
246.5	782.9	2.075	212.0	620.7	1.811	191.0	457.7	1.104
255.0	791.4	2.324	215.0	626.9	1.678	211.0	509.3	1.846
290.0	822.2	2.591	250.0	686.1	2.532	224.0	538.7	2.057
296.0	826.9	3.059	255.0	693.1	2.442	242.0	574.7	3.105
			280.0	724.2	3.616	266.0	615.3	4.653
			283.0	727.5	3.803	289.0	652.3	6.022
						296.0	657.1	7.087
				Nitrendipine				
117.0	414.4	0.566	100.0	221.2	0.134	121.0	244.4	0.269
129.5	502.2	0.686	117.0	284.8	0.291	136.0	288.9	0.782
142.0	569.1	1.341	126.0	322.8	0.237	142.0	307.7	1.163
158.5	631.3	1.693	139.0	380.6	0.440	173.5	406.6	2.173
168.0	658.2	1.855	150.0	429.0	0.700	191.5	457.7	2.648
179.0	684.1	2.190	162.0	477.9	0.960	205.0	494.6	3.421
190.0	705.9	2.325	173.0	517.2	1.545	218.0	525.6	4.316
200.0	723.1	2.367	186.0	557.4	2.078	227.0	549.8	4.641
217.0	748.1	2.524	206.0	607.8	2.769	241.0	572.8	5.995
226.0	759.6	2.815	214.0	624.8	3.236	261.0	603.1	6.995
239.0	774.8	3.077	229.5	653.9	3.689	283.0	640.0	8.970
246.0	782.4	3.517	242.0	674.2	4.245	300.0	662.0	10.586
259.0	795.3	3.642	281.0	725.3	5.640			
275.0	805.5	4.309	290.0	735.2	6.666			
300.0	829.9	4.903	300.0	749.3	7.063			

Table 3. Constants for the Solubility Correlation, Determined from the Plot log y vs log ϱ_r

	nifedipine		nitrendipine	
t/°C	θ	C_0	θ	C_0
60	3.75	−5.50	3.10	−5.17
80	3.87	−5.24	3.40	−4.95
100	4.03	−4.87	3.40	−4.53

with increasing temperature at constant density is also shown in Figure 4. The solubility isotherms are parallel or close to parallel because of the nonpolarity of nifedipine and nitrendipine.

The plot log y against ϱ_r is shown in Figure 5. Depending on the particular system, log y against log ϱ_r or log y against ϱ_r yields a linear plot. In the case of nifedipine in CO_2, better linearity is obtained in the plot log y against ϱ_r (Figure 5a) where the average absolute relative deviations of calculated and experimental data, AARD (%), at 60, 80, and 100 °C are 5.81, 9.63, and 12.50, respectively. For the plot log y against log ϱ_r (Figure 4a) the AARD (%) values at 60, 80, and 100 °C are 8.01, 12.03, and 21.54, respectively.

In the case of nitrendipine in CO_2, better linearity is also obtained in the plot log y against ϱ_r (Figure 5b) where the average absolute relative deviations of calculated and experimental data, AARD (%), at 60, 80, and 100 °C are 8.27, 9.02, and 16.83, respectively. For the plot log y against log ϱ_r (Figure 4b) the AARD (%) values at 60, 80, and 100 °C are 9.53, 15.88, and 17.16, respectively.

Chrastil's model suggests that plots of log c against log ϱ should yield parallel straight lines at different temperatures as presented in Figure 6. It can be seen from the plots that the linearity is better for nitrendipine ($R = 0.987$) than for nifedipine ($R = 0.723$).

In both binary systems, the slope of the solubility isotherms increases at higher temperature. This is an indication that the association constant is a function of temperature (Wells, 1990; Gurdial, 1991; Ting, 1993). In the case of nifedipine in CO_2, the correlation obtained in the plot log c against log ϱ (Figure 6a) the average absolute relative deviations of calculated and experimental data,

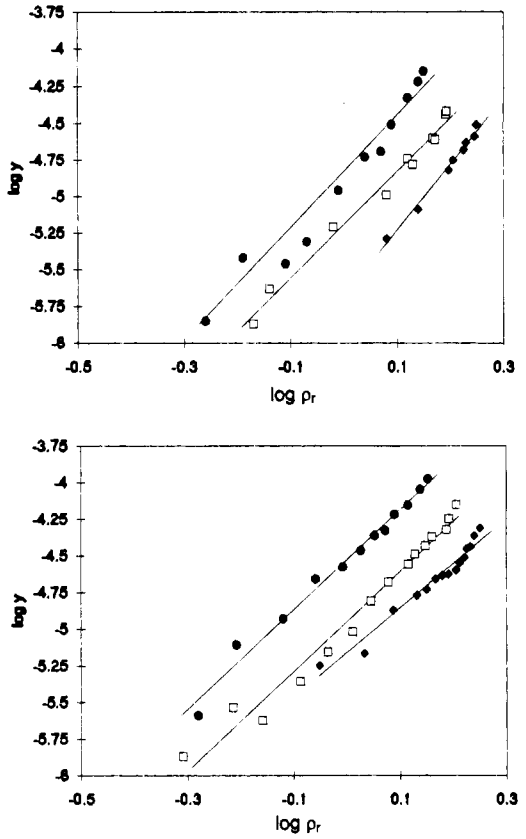

Figure 4. log y of (a, top) nifedipine and (b, bottom) nitrendipine as a function of log(reduced density): (♦) 60 °C, (□) 80 °C, (●) 100 °C.

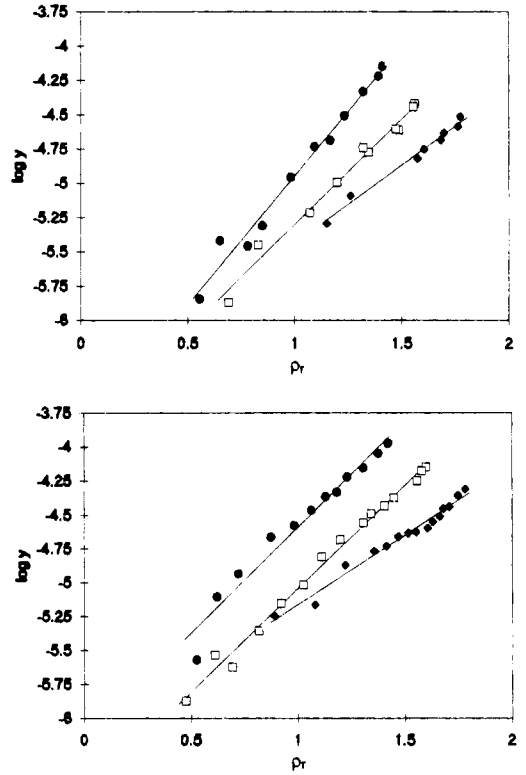

Figure 5. log y of (a, top) nifedipine and (b, bottom) nitrendipine as a function of reduced density: (♦) 60 °C, (□) 80 °C, (●) 100 °C.

AARD (%) at 60, 80, and 100 °C are 55.51, 26.29, and 29.42, respectively.

In the case of nitredipine in CO_2, the correlation obtained in the plot log c against log ϱ (Figure 6b) the average absolute relative deviations of calculated and experimental

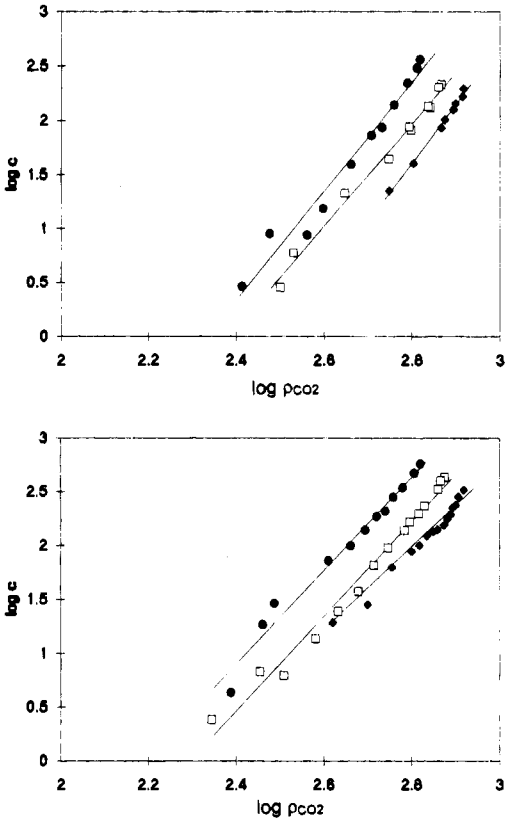

Figure 6. log c of (a, top) nifedipine and (b, bottom) nitrendipine as a function of log(density of CO_2): (♦) 60 °C, (□) 80 °C, (●) 100 °C.

data, AARD (%), at 60, 80, and 100 °C are 11.19, 17.62, and 23.77, respectively.

Conclusion

The solubilities of nifedipine and nitrendipine in carbon dioxide were determined for pressures ranging from 100 to 300 bar.

The mole fraction solubility of nifedipine rises at 60 °C from 0.51×10^{-5} (135 bar) to 3.1×10^{-5} (296 bar), at 80 °C from 0.14×10^{-5} (126 bar) to 3.8×10^{-5} (283 bar), and at 100 °C from 0.14×10^{-5} (126 bar) to 7.1×10^{-5} (296 bar).

The mole fraction solubility of nitrendipine rises at 60 °C from 0.57×10^{-5} (117 bar) to 4.9×10^{-5} (300 bar), at 80 °C from 0.13×10^{-5} (100 bar) to 7.1×10^{-5} (300 bar), and at 100 °C from 0.27×10^{-5} (121 bar) to 10.6×10^{-5} (300 bar).

The difference between the solubilities of nifedipine and nitrendipine is relatively very small due to their similar chemical structures and small difference in melting points and other physical properties.

Solubility data have been correlated with three density based models (log y against log ϱ_r, log y against ϱ_r, and log c against log ϱ), because application of equations of state have serious limitations due to the lack of physical properties of nifedipine and nitrendipine solubilized in CO_2.

The most successful model was log y against ϱ_r which correlates the solubility of both compounds the best.

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