Physicochemical Data on Ketoprofen in Solutions

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The solubility of ketoprofen in acetone + water as a function of temperature has been determined at the round temperature values 10−49 °C. The solubility diagram exhibits five regions: one homogeneous zone, three two-phase zones (two liquid−solid equilibria and one liquid−liquid equilibrium), and one three-phase zone. The density and viscosity as a function of concentration in the binary mixture ketoprofen + acetone are also reported. Some equations are proposed to correlate the experimental results.

Introduction

The racemic form of α-(3-benzoylphenyl)propionic acid (±) or ketoprofen ($C_{16}H_{14}O_3$) is a well-known anti-inflammatory agent. This product is dry and an irritant, and it causes sneezing, so the operator has to use a dust mask. It is stable if screened from light. It is not sensitive to temperature variations, but it may start to decompose above 340 °C. Solubility, density, and viscosity results for ketoprofen in acetone and its solubility in acetone + water are presented.

Experimental Section

Chemicals. Ketoprofen produced by Rhône-Poulenc Rorer Co., France, was used and had a minimum purity of 99.9%. The melting enthalpy, ΔH_m, and the melting temperature, t_m, of this solid have been obtained by differential scanning calorimetry (SETARAM DSC 92). They are respectively equal to (28 226 ± 254) J·mol^{-1} and (94.5 ± 0.5) °C. Synthesis grade acetone from Société de Distribution de Service et de Recherche had a minimum purity of 99.7%; these chemicals were used without further purification. Bidistilled water was used.

Solubilities. The solubility of ketoprofen was measured in water, acetone and acetone+water. Three experiments were carried out for each point.

The solubilities of ketoprofen in pure acetone and pure water were determined according to the procedure previously described (Mullin, 1972) consisting in periodically dissolving small amounts of solid ketoprofen in a stirred solution (25 cm^3 with acetone, 100 cm^3 with water) maintained at a constant temperature (t ± 0,1 °C). When ketoprofen does not appear to dissolve any more, the suspension is stirred for a few days more, during which the evolution of the concentration of ketoprofen in solvent is measured. The equilibrium is considered reached when the concentration remains constant. As the experiments with acetone proceed, loss of solvent due to evaporation is avoided by condensing the vapor.

Sampling of the solution for the measurement of the concentration of ketoprofen in solution is made by stopping the stirring of the suspension for 1 h to allow the remaining solid to settle. A 1−3 cm^3 sample of the solution is withdrawn with a syringe, filtered through a 0.45 μm porosity membrane at room temperature, and analyzed.

In the case of acetone, the sample is weighed and put in an oven at 50 °C; the concentration of ketoprofen is then deduced from the mass of the dry solid after complete evaporation of acetone. The accuracy of the measurements of the compositions was found to be ±0.9%.

A high-performance liquid chromatograph, Hewlett-Packard Series 1050 HPLC with wavelength detector and computing integrator, was used for the determination of ketoprofen concentration. The solution was chromatographed on a spherisorb C_{18} ODS2 (12.5 cm long with a 4 mm internal diameter) column using a mixture of water, acetonitrile, and phosphate buffer (68:40:2 v/v/v) as the mobile phase at ambient temperature, (25 ± 1) °C. The phosphate buffer is a solution of potassium dihydrogen phosphate (0.33 mol/dm^3) whose pH is adjusted to 3.5 with orthophosphoric acid. The detector wavelength was set at 280 nm. The flow rate of the mobile phase is 1.5 mL·min^{-1}. A 5 × 10^{-3} cm^3 volume of the sample solution was injected. The accuracy of analysis for HPLC was found to be about 3.5% between 10 and 20 °C. However, this accuracy has been evaluated to 12% at 30 °C. This maximum can be explained by the difference between the solution temperature (30 °C) and the room temperature which can induce crystallization of the drug during sampling. However, it can be noticed that absolute deviations are only a few hundred ppm concentrations.

With the ternary system ketoprofen + acetone + water, three equilibrium types were observed; hence, three analytical procedures were used.

The first one is the dissolution procedure previously described for liquid−solid equilibria in pure solvents.

The second one is a settling procedure for liquid−liquid equilibria. An acetone + water + ketoprofen mixture of about 100 cm^3 is stirred continuously for 1 h in a reactor at a constant temperature controlled to better than ±0.1°C. After 1 h of agitation, this mixture is poured into a thermostated settling flask. After 24 h of settling, the aqueous and organic phases are separated and stored. The concentration of ketoprofen is determined from the mass of the dry extract. The determination of the water content is carried out by using the Karl Fisher titrator method. A Mettler DL18 Karl Fisher titrator is used. The accuracy of these measurements was found to about 4%.

The third procedure used is a specific procedure for liquid−liquid−solid equilibria. An acetone + water + ketoprofen mixture of about 100 cm^3 is also continuously stirred for 1 h in a reactor at constant temperature. The system is allowed to separate and settle. The reactor is a small double jacketed glass vessel with facilities for sampling a few cm^3 of the solution with syringes at various levels. So, syringes permit samples of the two liquid phases to be taken simultaneously without disturbing the equilibrium.

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Table 1. Experimental Solubility as the Mass Fraction w of Ketoprofen (1) + Acetone (2) + Water (3)[a]

Liquid–Solid Equilibria

t/°C	w_1	w_2*	t/°C	w_1	w_2*
9.8	0.000 086	0	30.0	0.000 225	0
	0.000 105	0.023		0.000 261	0.017
	0.000 199	0.072		0.000 261	0.026
	0.000 623	0.151	30.9	0.550	0.669
	0.002 182	0.219		0.577	0.730
10.1	0.410	0.727		0.596	0.747
	0.427	0.773		0.589	0.796
	0.444	0.811		0.576	0.896
	0.447	0.888		0.602	0.902
	0.423	0.906		0.589	0.934
	0.447	0.960	29.9	0.513	1
	0.416	0.967	41.1	0.613	1
9.8	0.360	1	48.9	0.703	0.852
20.1	0.000 124	0	49.3	0.710	0.924
	0.000 151	0.016		0.701	0.950
	0.000 177	0.024		0.695	0.967
	0.000 337	0.072		0.677	1
	0.001 410	0.163			
20.3	0.498	0.755			
	0.517	0.796			
	0.529	0.868			
	0.502	0.910			
	0.510	0.941			
	0.487	0.961			
19.8	0.431	1			

Liquid–Liquid Equilibria

	aqueous phase		organic phase	
t/°C	w_1	w_2*	w_1	w_2*
10.0 ± 0.1	0.089	0.474	0.304	0.657
20.0 ± 0.1	0.058	0.399	0.358	0.649
20.9 ± 0.1	0.087	0.438	0.305	0.626
20.7 ± 0.1	0.098	0.458	0.287	0.600
20.6 ± 0.1	0.118	0.475	0.276	0.610
30.4 ± 0.1	0.058	0.367	0.359	0.624

Liquid–Liquid–Solid Equilibria

	pure solid		aqueous phase		organic phase	
t/°C	w_1	w_2*	w_1	w_2*	w_1	w_2*
10.1 ± 0.1	1	0	0.073	0.462	0.269	0.606
20.0 ± 0.1	1	0	0.021	0.243	0.482	0.672
30.0 ± 0.1	1	0	0.036	0.342	0.452	0.646

[a] w_2* is the mass fraction of acetone in the initial acetone (2) + water (3) solution.

The results are expressed in kilograms of solute per kilogram of solution and are given in Table 1 for the binary and ternary mixtures studied and reported in Figure 1. w_2* corresponds to the mass fraction in the initial acetone (2) + water (3) solutions. The diagram exhibits five regions: one homogeneous zone, three two-phase zones (two liquid–solid equilibria and one liquid–liquid equilibrium), and one three-phase zone (liquid–liquid–solid).

The points with zero acetone concentration and with zero water concentration show that the solubilities of ketoprofen in the pure solvent increase when temperature increases. These solubilities are high in pure acetone and very low in pure water.

In the case of the ternary system, in the liquid–solid regions, the solubility of ketoprofen (1) increases with temperature. For a low mass fraction of acetone (2) (w_2* < 0.22), the solubility of the drug increases with this mass ratio. Liquid–liquid zones are obtained for mass fractions in the range 0.22–0.67. When w_2* is higher than 0.67, the solubility reaches a maximum for a value of w_2 between 0.86 and 0.93.

Densities. The density of ketoprofen crystals has been measured by means of a pycnometer in the presence of a nonsolvent (ethylbenzene) for a temperature of 20 °C. The obtained value is 1160 kg·m^{-3}.

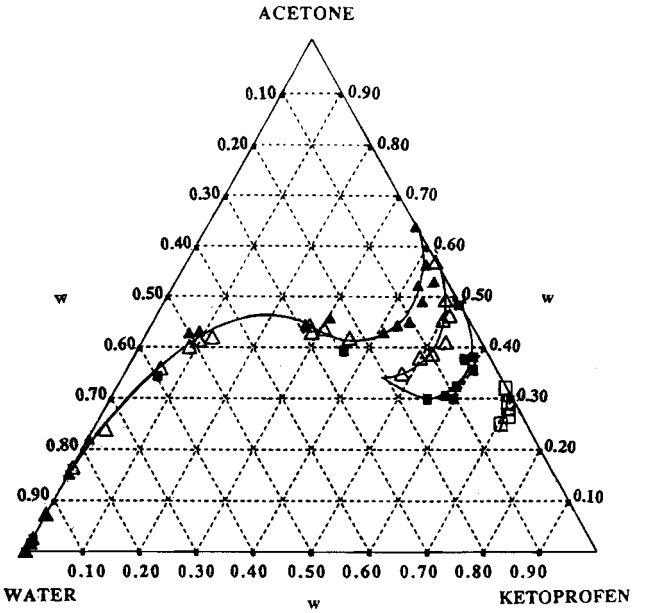

Figure 1. Solubility of ketoprofen in acetone (2) + water (3) solutions at 10.1 (▲), 20.2 (△), 30.2 (■), and 48.9 (□) °C.

Table 2. Experimental Densities for the Binary System Ketoprofen (1) + Acetone (2) at 20.0 °C versus Mass Fraction w_1

w_1	ϱ/(kg·m^{-3})	w_1	ϱ/(kg·m^{-3})
0	790	0.321	917
0.108	825	0.426	928
0.213	896	1	1160

The densities of ketoprofen + acetone mixtures were determined using a 30 × 10^{-6} m^3 pycnometer at 20 °C. The clean and dry pycnometer is weighed before each experiment with an accuracy of ±0.0001 g. The density is found by dividing the difference between the mass of the full and the empty pycnometer by the calibrated pycnometer volume. Solutions were prepared by dissolving a known amount of ketoprofen in a known mass of pure acetone. The maximum concentration of ketoprofen in solution is lower than the solubility at 20 °C. The estimated error on the mass fraction w_1 is ±2.4 × 10^{-6}. The accuracy of the measurements of the densities was found to be ±1.4%.

Density experiments are listed in Table 2. If the dissolution of ketoprofen crystals in the solvent took place at constant molecular volumes, it would be possible to predict the density of the solution by

$$\frac{1}{\varrho} = \frac{w_1}{\varrho_1} + \frac{1 - w_1}{\varrho_2} \qquad (1)$$

where ϱ_1 is the density of the crystals of ketoprofen and ϱ_2 is the density of acetone.

These variations of density as a function of concentration at 20.0 °C, given by the theoretical correlation (1), are also reported in Figure 2. The experimental values are higher than the calculated ones. However, the maximum difference observed is lower by 5.5%. The discrepancy can be explained by the assumption on the addition of the volumes. In fact, the dissolution of ketoprofen in acetone occurs with a decrease of the total volume.

Viscosities. The rheological behavior of the solutions has been studied. A saturated solution was prepared at 50 °C, with a mass fraction of 0.653. This solution was cooled to 23 °C and placed between two coaxial cylinders

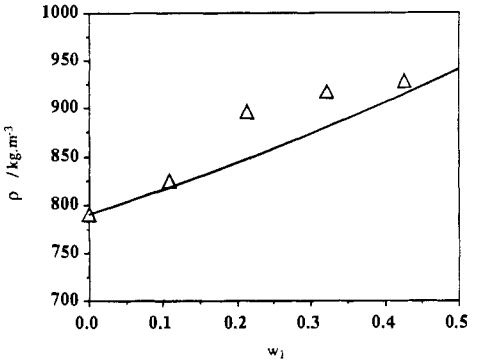

Figure 2. Density of the binary system ketoprofen (1) + acetone (2) as a function of mass fraction w_1: (△) experimental data, at 20.0 °C; (—) data calculated from eq 2 at 20.0 °C.

of a viscosimeter. The internal cylinder revolves with a constant velocity, v_x, and the external cylinder is fixed. The shear stress, τ_{xy}, as a function of the shear rate, $\dot{\gamma}$ (with $\dot{\gamma} = dv_x/dy$), leads to the rheological law followed by the solution. Units of shear stress and shear rate are, respectively, Pa and s^{-1}. Under Newton's law, viscosity is independent of shear stress. The absolute viscosity of a Newtonian fluid is equal to the slope of the shear stress–shear rate curve.

In our case, since the shear stress is a linear function of the shear rate, the solutions ketoprofen (1) + acetone (2) can be considered as Newtonian and the viscosity of the solution measured by this method is equal to 13.5×10^{-3} Pa·s. As a consequence, the viscosity of the ketoprofen + acetone with a mass fraction equal to 0.426 has been determined from the terminal velocity of a falling sphere at 20.0, 25.2, 30.0, and 36.0 °C. The viscosities of the solutions with mass fractions in the range 0.108–0.426 have been measured at 20 °C. The solutions were prepared in the same way as for density determination. The accuracy of the measurements of the viscosities was found to be ±1.0%.

Table 3. Experimental Viscosity of the Binary System Ketoprofen (1) + Acetone (2) versus Temperature and Mass Fraction w_1

t/°C ± 0.1	w_1	η/(mPa·s)	t/°C ± 0.1	w_1	η/(mPa·s)
20.0	0.108	0.621		0.653	13.5
	0.213	0.843	25.2	0.426	1.08
	0.321	1.173	30.0	0.426	0.97
	0.426	1.372	36.0	0.426	0.88

The results as a function of temperature and concentration of ketoprofen (1) are given in Table 3. The data can be correlated by the equations

$$\eta/(\text{mPa·s}) = 0.46 \times 10^{(3.375 \times w_1^2)} \quad (2)$$

with a coefficient of correlation equal to 0.98 and

$$\ln \eta/(\text{Pa·s}) = -14.8 + \frac{2.0 \times 10^4}{R(T/\text{K})} \quad (3)$$

with a coefficient of correlation equal to 0.97.

Literature Cited

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