Pharmaceutical Research, Vol. 6, No. 2, 1989

Report

Solubility Behavior of Narcotic Analgesics in Aqueous Media: Solubilities and Dissociation Constants of Morphine, Fentanyl, and Sufentanil

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Received June 30, 1988; accepted August 29, 1988

The pH dependence of the aqueous solubility of morphine, fentanyl, and sufentanil was investigated at 35°C. Dissociation constants and corresponding pK_a' values of the drugs were obtained from measured free-base solubilities (determined at high pH's) and the concentrations of saturated solutions at intermediate pH's. Morphine, fentanyl, and sufentanil exhibited pK_a' values of 8.08, 8.99, and 8.51, respectively. Over the pH range of 5 to 12.5 the apparent solubilities are determined by the intrinsic solubility of the free base plus the concentration of ionized drug necessary to satisfy the dissociation equilibrium at a given pH. Consequently, the drug concentrations of saturated aqueous solutions fall off precipitously as the pH is raised and ionization is suppressed. Further, at low pH's the aqueous solubility of morphine increased in a linear fashion with increases in the molar strength of citric acid which was added to acidify the medium, suggesting the formation of a soluble morphine–citrate complex.

KEY WORDS: narcotic analgesics; dissociation constants; pH–solubility profiles; solubility; amines.

INTRODUCTION

Naturally occurring opioid alkaloids such as morphine and synthetic 4-anilinopiperidine analogues such as fentanyl and sufentanil (see Fig. 1) are used for the relief of postsurgical pain, chronic cancer pain, and other pain (1). These drugs are commonly given orally and parenterally; however, many of the narcotics are relatively short acting, necessitating frequent administration, with widely fluctuating blood levels. Therefore, it is desirable to attain steady plasma levels over long time periods. Transdermal delivery may represent a suitable delivery route.

Skin permeation studies are generally performed using aqueous vehicles. The rate of delivery of a drug from its vehicle through the skin is directly proportional to the drug's concentration. The maximum achievable rate and the rate used to determine delivery feasibility are therefore set by the drug's solubility in the aqueous vehicle and, if the drug is a weak electrolyte, by its state of ionization (2–6). Thus, to interpret permeation data and choose the best conditions for delivering drugs as the weakly basic narcotics, one has to know their solubilities and dissociation tendencies in water in addition to their solubilities in organic media (7). This information, coupled with permeability coefficients, predicts drug penetration through skin. Therefore, the aqueous solubilities of morphine, fentanyl, and sufentanil have been investigated as a function of pH. The equilibrium of an organic base with water may be expressed in terms of the dissociation of its conjugate acid by (8–11)

$$BH^+ + H_2O = B + H_3O^+ \quad (1)$$

The mass law expression for the equilibrium takes the logarithmic form:

$$pK_a' = pH + \log \frac{[BH^+]}{[B]} \quad (2)$$

At pH's where the free base is saturated, this can also be written as

$$pK_a' = pH + \log \left(\frac{C_T - [B_s]}{[B_s]} \right) \quad (3)$$

where C_T is the total concentration of a saturated solution of arbitrary pH and $[B_s]$ is the free-base solubility. This equation was used to calculate pK_a' values from the equilibrium solubilities of morphine, fentanyl, and sufentanil at various intermediate pH values (11).

MATERIALS AND METHODS

Materials. Fentanyl and sufentanil were a gift from Janssen Pharmaceutica (N.J.) and were used as received. Morphine sulfate and codeine phosphate (internal standard in the assay) were requisitioned from the University of Michigan Hospital (Ann Arbor). Morphine free base was liberated from aqueous solutions of morphine sulfate by adding an

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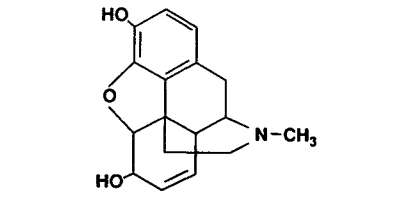
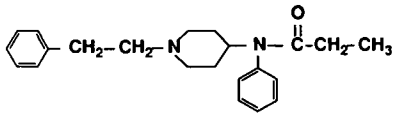


MORPHINE



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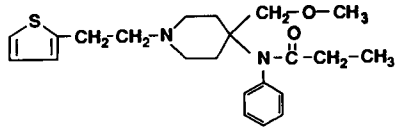

SUFENTANIL

Fig. 1. Chemical structures of morphine, fentanyl, and sufentanil.

aliquot of a saturated solution of sodium bicarbonate and then extracting the morphine base with methylene dichloride. The organic phase was collected and evaporated to dryness under a gentle stream of dried nitrogen. Morphine base was recrystallized from hexane:ethanol (95:5). The purity of the crystalline solid was determined by high-performance liquid chromatography (HPLC) and by its melting point. Double-distilled deionized water was used to prepare the buffered media for the solubility studies. Buffers were prepared from reagent-grade chemicals.

Chromatographic Procedures. Morphine was assayed by HPLC using UV detection at 254 nm. A μ-Bondapak C_{18} column (Waters Associates) and a mobile phase of acetonitrile–water (26:74) provided good chromatographic resolution. The same procedure was used as described by Kubiak and Munson (12). Calibration curves were obtained by plotting the peak height ratio of the authentic drug to the internal standard (codeine) as a function of the drug concentration in the standard aqueous sample. Standard curves demonstrated excellent linearity over the concentration range employed.

Fentanyl and sufentanil were assayed by gas chromatography (GC). The gas chromatograph (Hewlett Packard GC-5840) was equipped with a flame ionization detector. Aqueous samples were basified with 0.5 *M* NaOH and the internal standard was added. These solutions were then extracted with hexane:95% ethanol (95:5). The organic solvent was separated and evaporated to dryness. The residue was reconstituted in 20 μl of hexane and an aliquot of 2 μl was injected into the GC. A glass column (182 × 0.2 cm) packed with 3% OV-17 and maintained at 282°C was used. The detector and injector temperatures were 300°C and a nitrogen flow rate of 35 ml/min was used. Peak areas were automatically integrated with an integrator (HP-1885). Representative chromatograms for morphine, fentanyl, and sufentanil using these assays have been published (7).

Solubility Determinations. The solubilities of morphine, fentanyl, and sufentanil in aqueous media were determined by equilibrating large excesses of the solutes with citrate–phosphate buffers of varied pH's at 35°C. The buffers used are given in Table I. At the end of the equilibration period, samples were drawn and filtered through Millipore filters (Fluoropore, 0.22-μm Millipore) attached to the ends of glass syringes. Aliquots for determining the concentrations of the samples were transferred to test tubes. In order to avoid adsorption of drug by the filter paper, the initial filtrate (25% of the total filtrate) was discarded and subsequent filtrate was collected for the solubility determinations. All sampling operations were carried out at or above 35°C to prevent precipitation of the solute within the filtered samples prior to diluting them for assay. The aqueous samples were either extracted with organic solvents for GC assay or assayed directly by HPLC. Three samples were drawn from the saturated slurries at each pH. Concentration versus time of equilibration plots (Fig. 2) indicated that equilibrium was obtained well within 48 hr. Therefore, all samples were equilibrated minimally for 48 hr. The pH's associated with the solubility data were measured after reaching equilibrium.

Table I. Buffer Compositions

Initial pH	*x* ml of 0.1 *M* citric acid	*y* ml of 0.2 *M* Na_2HPO_4
2.6	89.10	10.90
3.0	79.45	20.55
4.0	61.45	38.55
4.6	53.25	46.75
5.0	48.50	51.50
5.6	42.00	58.00
6.0	36.85	63.15
6.6	27.25	72.75
7.0	17.65	82.35
7.6	6.35	93.65

RESULTS

Solubilities of morphine at 35°C in buffered, aqueous media as a function of pH are provided in Table II. These values are the means of three determinations, all with coefficients of variation <5%. Over the pH range studied, the free base is saturated. Its contribution to solubility is small at

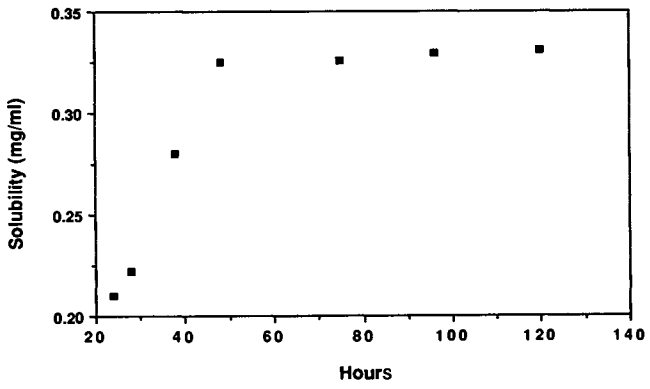

Fig. 2. Kinetics of formation of a saturated solution of morphine at 35°C in water. The slight upward drift at a long time was concurrent with slight decrease in pH.

Table II. Aqueous Solubility of Morphine at 35°C as a Function of pH in Citrate–Phosphate Buffer

pH of solubility measurement	Solubility (mg/ml)
5.67	65.18
5.77	64.61
5.84	56.24
5.91	44.28
5.95	37.84
6.05	28.76
6.15	24.09
6.24	19.65
6.35	13.39
6.69	5.75
7.13	2.00
7.45	1.14
7.85	0.41
7.99	0.37
8.61	0.25

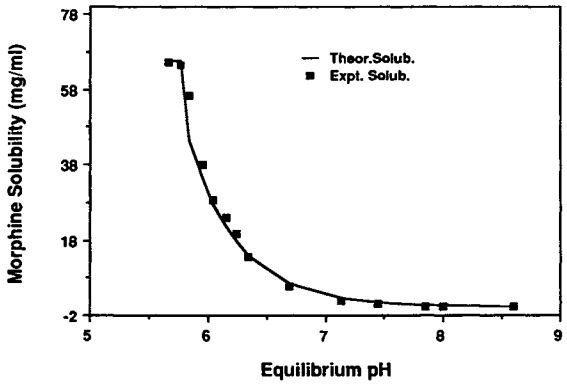

Fig. 4. Solubility of morphine in water at 35°C as a function of pH. The line drawn through the data is a theoretical curve and was calculated using 0.25 mg/ml as the free-base solubility and 8.08 as the pK_a'.

and below pH 8.0 due to extensive ionization of the drug. The solubility of morphine's free base obtained from the average solubility above pH 8.6 was 0.25 mg/ml. The solubility of morphine citrate was estimated to be 64.9 mg/ml below pH 5.80. Morphine's solubility was actually increased by the presence of citrate in the buffered media. The linear relationship between the molar strength of citric acid and morphine citrate's solubility at pH 5.6 is shown in Fig. 3.

The solubility–pH curve for morphine is depicted in Fig. 4. The theoretical profile for morphine in aqueous media in Fig. 4 was computed using Eq. (3), after determining the pK_a' and free-base solubility. The mean pK_a' of morphine was determined from its total solution concentration at saturation at different pH values and the estimated free-base solubility [Eq. (3)] and is 8.08 ± 0.06 (N = 9).

It was not clear if morphine was sufficiently chemically robust to have its solubility assessed at all pH's. Therefore, some limited stability studies were performed. The degradation of morphine as a function of pH at 45°C is shown in Fig. 5. No appreciable morphine degradation occurred within 48 hr, the time period used to establish equilibrium.

The solubilities of fentanyl and sufentanil in water at 35°C are listed in Tables III and IV, respectively, in the order of increasing pH. In each case, the solubility decreased exponentially as the pH increased (Figs. 6 and 7). Free-base solubilities of 9.9×10^{-3} and 1.2×10^{-3} mg/ml, respectively, were obtained for fentanyl and sufentanil. Theoretical solubility profiles were again computed from Eq. (3) from the estimated pK_a' and free-base solubility. These theoretical profiles satisfactorily fit the solubility data, with one exception. Sufentanil's solubility below pH 5 was low relative to projection. This is a region where one can expect common ion (citrate anion) suppression of the solubility.

In Table V, pK_a' values for morphine, fentanyl, and sufentanil determined by two different data reduction methods are compared against literature values. In addition to averaging pK_a's determined at each pH [Eq. (3)], the pK_a's were determined graphically by plotting pH versus log $([B]_{sat}/[BH^+])$ [Eq. (2)]. Straight lines were obtained which theoretically intercept at the pK_a's (13). The pK_a's of morphine determined by solubility and graphical methods are all virtually the same as reported in the literature. However, the pK_a's of fentanyl and sufentanil differ by as much as 0.8 pK_a' unit from previously reported values.

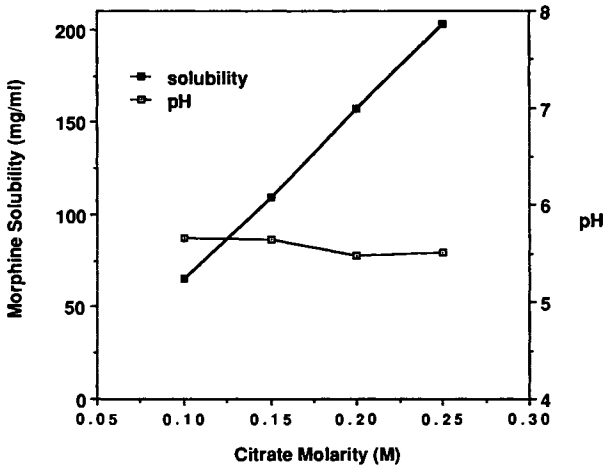

Fig. 3. Solubility of morphine in water at 35°C as a function of molar strength of the citric acid at pH ≈5.5.

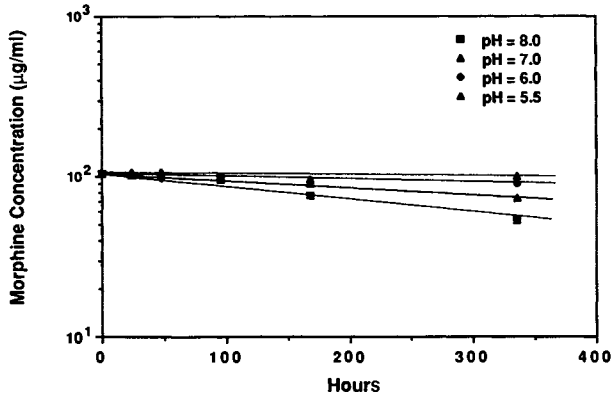

Fig. 5. Effect of pH on degradation of morphine at 45°C over a 15-day period. The decrease in morphine concentration in 2 days is hardly measurable.

Table III. Aqueous Solubility of Fentanyl at 35°C as a Function of pH in Citrate–Phosphate Buffer

pH of solubility measurement	Solubility (mg/ml)
5.48	75.13
5.57	56.41
5.79	29.57
5.94	13.32
6.23	5.25
6.51	2.49
7.04	0.74
7.66	0.28
8.03	0.067
8.78	0.009
9.80	0.008
12.47	0.012

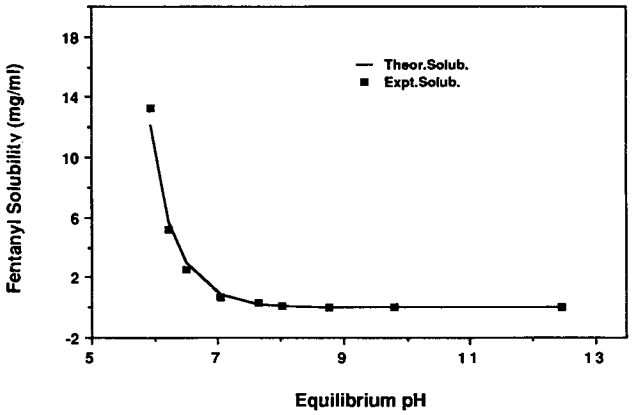

Fig. 6. Solubility of fentanyl in water at 35°C as a function of pH. The line drawn through the data is a theoretical curve and was calculated using 9.9×10^{-3} mg/ml as the free-base solubility and 8.99 as the pK_a'.

DISCUSSION

pK_a's of Morphine, Fentanyl, and Sufentanil. Morphine's literature pK_a' is 8.3 at 25°C (14). This pK_a' value was determined potentiometrically in methanol–water mixtures. Methanol was used to raise morphine's total concentration to titratable levels and the pK_a' value reported for its dissociation in pure water was obtained by extrapolation. Because solvents affect ionization in ways which are not entirely predictable, pK_a's determined in this fashion are prone to misestimation.

The pK_a' of a weak electrolyte can also be deduced from solubility data. For example, the pK_a' can be determined by the plotting technique mentioned in results. A 35°C value of 8.07 was arrived at for morphine using this technique (r^2 = 0.99). In order to compare values, the 25°C literature pK_a' of morphine was corrected to 35°C using the following equation (15):

$$\frac{-d(pK_a')}{dT} = \frac{pK_a'_{(25°)} - 0.9}{T} \qquad (4)$$

where the temperature, T, is in degrees absolute. According to Eq. (4), the pK_a' of a basic compound decreases as the temperature increases. It follows that an increase in temperature from 25 to 35°C reduces the pK_a' value of morphine by about 0.25 unit. The pK_a' of morphine at 35°C corrected from the 25°C literature value turns out to be 8.05, virtually identical to the value obtained by the graphical method (Table V). The pK_a' of morphine was also estimated from the apparent solubility at each pH and its 35°C free-base solubility, 0.25 mg/ml (11). Individually determined pK_a's were then averaged to arrive at a pK_a' of 8.06 ± 0.06 for morphine, which is within 0.1 pK_a' unit of the other estimates.

The pK_a' values of fentanyl and sufentanil were similarly determined. Potentiometrically determined, 25°C pK_a' values of these compounds from the literature were 8.43 and 8.01, respectively (16). As with morphine, the pK_a's were adjusted to 35°C using Eq. (4). The pK_a's of fentanyl and sufentanil estimated from the solubility data are presented in Table V side by side with the literature values. The pK_a' values for fentanyl and sufentanil from solubility data were 8.99 ± 0.13 and 8.51 ± 0.22, respectively. In each instance, literature pK_a' values were about 0.8 pK_a' unit lower, 8.18 and 7.77, respectively.

Solubilities of Morphine, Fentanyl, and Sufentanil. The solubility profile for morphine in 0.1 *M* citrate–phosphate buffer is given in Fig. 4, with an estimate of 0.25 mg/ml of the free-base solubility of morphine at 35°C. This

Table IV. Aqueous Solubility of Sufentanil at 35°C as a Function of pH in Citrate–Phosphate Buffer

pH of solubility measurement	Solubility (mg/ml)
3.04	38.07
4.34	14.09
5.31	3.93
5.66	1.51
6.15	0.57
6.45	0.16
6.64	0.11
6.97	0.025
7.60	0.010
7.98	0.0033
8.73	0.0012
12.77	0.0013

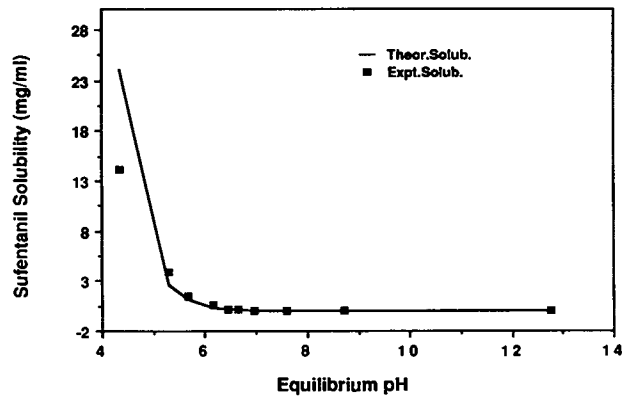

Fig. 7. Solubility of sufentanil in water at 35°C as a function of pH. The lines drawn through the data is a theoretical curve and was calculated using 1.2×10^{-3} mg/ml as the free-base solubility and 8.51 as the pK_a'.

Table V. The pK_a' Values of Morphine, Sufentanil, and Fentanyl at 35°C

Drug	Solubility method	Graphical method	Reported[a]
Morphine	8.08 ± 0.06 (9)[b]	8.07	7.95[c]
Sufentanil	8.51 ± 0.22 (9)	8.50	7.77[d]
Fentanyl	8.99 ± 0.13 (8)	8.73	8.18[d]

[a] Corrected to 35°C.
[b] Value in parentheses indicates number of determinations.
[c] From Ref. 15.
[d] From Ref. 16.

value is lower than the reported solubility (7) because ionization, which is unavoidable when a free base is simply dissolved in water, is factored out. With the aid of this information, one can determine the intrinsic permeability coefficient of morphine through lipophilic membranes such as the skin, from apparent permeability coefficients.

In an attempt to determine the solubility of morphine citrate, excess morphine base was added to citric acid solutions of increasing concentrations with the expectation that, discounting common ion effects, a level saturation concentration would eventually be achieved. Because of the common ion effect, it was anticipated that, if anything, the solution concentration of morphine from its saturated salt would be suppressed with increasing citrate concentrations. Somewhat surprisingly, we were unable to determine an upper limit on morphine's solubility in concentrated citric acid media within the limits of the available compound, Moreover, the "apparent solubility" increased linearly with the total citrate concentration ($y = 922.4\,x - 27.6$; $r^2 = 0.99$) without there being appreciable shifts in pH, as shown in Fig. 3. The solubility of morphine changes by 3.2 mol/liter per unit change in the citrate molarity, a factor corresponding roughly to a 3-to-1 complex. This result suggests that morphine forms soluble, solution complexes in the acidic citrate medium. The solution concentration apparently reflects ionized morphine plus a considerable amount of complexed morphine. Previous workers have discussed the possibility that morphine self-associates (17,18). The presence of citrate had no apparent effect on morphine's solubility at the higher pH's used to determine the pK_a'.

Solubility profiles for fentanyl and sufentanil in citrate–phosphate buffer (Figs. 6 and 7) were qualitatively similar to that of morphine. Except for pH values below 5.5, the solubility profiles for all three narcotics are described by Eq. (3). The free-base solubilities used in the equation were 9.9×10^{-3} and 1.2×10^{-3} mg/ml for fentanyl and sufentanil, respectively. Sufentanil's low aqueous solubility reflects the fact that it is more hydrophobic than fentanyl (7). The low aqueous solubilities of the two 4-anilinopiperidine compounds also reflects a contrast in polarity between the different narcotic classes. Morphine is more water soluble and less soluble in all other solvents tested (7).

ACKNOWLEDGMENTS

The authors wish to thank Janssen Pharmaceutica, N.J., for their generous donation of fentanyl and sufentanil for the work. This work was supported by NIH Grant DA-046061. Part of this work was presented at the American Association of Pharmaceutical Scientists 1st National Meeting, Washington, D.C., November 1986.

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