A Solubility and Related Physicochemical Property Comparison of Buprenorphine and Its 3-Alkyl Esters

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Received April 11, 1995; accepted June 7, 1995

KEY WORDS: buprenorphine; regular solution theory; solubility parameter; solubility.

INTRODUCTION

Improved pharmacotherapies for opioid addiction treatment are urgently needed to maintain opioid addicts in treatment and away from high-risk tuberculosis (TB) and HIV/AIDS transmission behavior associated with the intravenous abuse of this class of drugs (1, 2). Buprenorphine, a synthetic partial agonist-antagonist opioid, has proven clinically effective in reducing illicit opioid use and maintaining patients in treatment when it is given sublingually at a high dose of 8 mg per day (3). Buprenorphine is also an analgesic in its own right and has been used i.v. and i.m. in human therapy at one-fourth or less of this dose for some time (4). Interestingly, all its dosage forms are associated with rapid systemic delivery, offering potential addicts the capability of getting a rapid "high", favoring buprenorphine's illicit use. An administration means which meters the drug slowly into the body, smoothing out blood levels and obviating serum highs, is desirable. From this standpoint, a transdermal delivery system seems an ideal way to administer buprenorphine. Sustained transdermal delivery, often zero order, averts peaks and valleys in serum levels associated with both oral and parenteral dosing. However, buprenorphine's high level of crystallinity as reflected in the melting point of its free base, 218°C, makes it unlikely it can be delivered transdermally at the dose required for opioid maintenance therapy. Prodrugs of buprenorphine with properties more suited for the delivery method might be effective, however, and we have synthesized compounds (Figure 1) with this reasoning in mind.

The physicochemical properties of drugs, especially their solubilities, are crucial to decisions about and the design of novel systems of delivery (5). Generally, the greater a drug's innate tendencies to dissolve, the more likely it is that the drug can be delivered at an adequate rate across any membrane, including the skin (6, 7). The concentration of drug that can build in the stratum corneum, the skin's principal barrier element, bears some relationship to the solubility of the drug in organic solvents such as hexane because the diffusion conduit through this barrier is itself lipoidal. Therefore, the hexane solubilities of buprenorphine and several potential prodrugs have been assessed and compared, along with several important physicochemical determinants of solubility, including their melting points, and heats of fusion.

THEORETICAL BACKGROUND

Regular Solution Analysis

Providing heat capacities are temperature independent, the thermodynamic activity of a crystalline solute, a_2, is exactly related to its reference super-cooled liquid state through the following equation (8):

$$\ln a_2 = \frac{-\Delta H_f}{RT}\left(\frac{T_f - T}{T_f}\right) + \frac{\Delta C_p}{R}\left(\frac{T_f - T}{T_f}\right) - \frac{\Delta C_p}{R}\left(\ln \frac{T_f}{T}\right) \quad (1)$$

where ΔH_f is the heart of fusion of a solid having a melting point, T_f, T is any experimental temperature less than T_f, and R is the gas constant. ΔCp is the difference in heat capacity, at constant pressure, between the crystalline solid and the hypothetical super-cooled liquid state of a compound. Since ΔCp is small and the absolute difference in the last two terms smaller yet (9–11), the equation is often seen as the familiar and relatively accurate approximation:

$$\ln a_2 = \frac{-\Delta H_f}{RT}\left(\frac{T_f - T}{T_f}\right) \quad (2)$$

In general, a substance's activity and concentration are relatable through an activity coefficient i.e. $a_1 = \gamma_i C_i$, and it follows that the thermodynamic activity of a crystalline organic solute, a_2, can be related to its saturation concentration in a specific solvent through:

$$a2 = \gamma_2 X_2 \quad (3)$$

where γ_2 is the solute's activity coefficient and X_2 is its mole fraction solubility. Since the activity coefficient of an ideal solution is unity (by definition), the thermodynamic activity, a_2, also represents the mole fraction ideal solubility. However, solutes rarely exhibit ideal behavior in real solvents. When the nonideality arises strictly from differential cohesiveness, which occurs when dispersion forces alone are involved, a solid solute in equilibrium with its saturated solution is related to its mole fraction solubility according to a relationship referred to as the regular solution equation (8):

$$\ln X_2 = \frac{-\Delta H_f}{RT}\left(\frac{T_f - T}{T_f}\right) - \frac{V_2 \phi_1^2}{RT}(\delta_1 - \delta_2)^2 \quad (4)$$

where δ_1 and δ_2 are the solubility parameters or square-roots of the cohesive energy densities of the solvent (given the subscript 1) and solute (given the subscript 2), V_2 is the molar volume of the solute, and ϕ_1 is the volume fraction of the solvent. This equation indicates that if one knows the solubility of an organic solute in an apolar organic solvent like hexane, the solute's heat of fusion, the solute's melting

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0724-8741/95/1000-1526$07.50/0

point, and the solubility parameter of the solvent, the solubility parameter of the solute can be calculated (10, 11).

MATERIALS AND METHODS

Materials

Buprenorphine HCl and base were purchased from Unichem Laboratories, India and AKZO (Diosynth), The Netherlands. Identification and purity of the batches were assured through high-pressure liquid chromatography (HPLC) retention times and thermal data. The alkyl esters were synthesized directly from buprenorphine. High levels of purity (>98%) were assured through elemental analysis, ^{1}H-NMR spectroscopy, HPLC and by the sharpness of melting points. Reagent-grade organic solvents were used as received.

Synthetic Method

Aliphatic esters of buprenorphine were prepared from the hydrochloride salt of buprenorphine in a two-step procedure. The buprenorphine hydrochloride salt was first treated with one equivalent of triethylamine to liberate the free base, and then this was reacted with the respective aliphatic acid anhydride in the presence of dimethylaminopyridine, which scavenged liberated aliphatic acid. The progress of the esterification reaction was monitored by TLC on silica gel GF plates (ethyl acetate:hexane, 2:3). The resulting alkyl-esters were purified by silica gel column chromatography (ethyl acetate:hexane, 2:3). The ^{1}H-NMR of the final products (phenolates) shows the disappearance of the resonance at 5.3 PPM, which has been assigned to the phenolic proton of buprenorphine. The HPLC profile of each ester showed a single peak at 254 nm. Carbon, hydrogen, nitrogen analysis was within ±0.2% for the acetyl, propyl, butyl and isobutyl esters. Elemental analysis was not done for the pentyl, hexyl, or heptyl esters, because it was considered superfluous to analyze compounds that don't differ from the parent compound in weight percentages greater than the intrinsic error of the analytical test. The ^{1}H-NMR spectroscopy, HPLC retention times and sharpness of melting points were considered more critical for characterization of these compounds.

Specifically, to buprenorphine hydrochloride (0.46 g, 0.9 mmol) suspended in 20 ml of methylene chloride, cooled to 0°C in an ice bath, triethylamine (0.9 mmol, 1 eq) was added slowly. The reaction mixture was stirred for 1 hour at this temperature. The organic layer was washed with 2 × 20 ml of water, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give 0.4 g of buprenorphine free base. The product was a white solid in near quantitative yield (94%) with a melting point of 216-219°C (buprenorphine base).

The free base of buprenorphine (0.85 mmol) obtained from the above reaction was dissolved in 25 ml of dry dimethylformamide and 1.2 equivalent of the appropriate acid anhydride. Eighty-five hundredths of a mmol of 4-dimethylaminopyridine (1 eq) was added. The reaction mixture was heated at 80°C for 4 hours and then cooled to room temperature and partitioned between water and ethyl acetate. The organic layer was separated, washed repeatedly with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the respective crude alkyl-esters of buprenorphine. The crude esters were purified by gravity silica gel column chromatography (ethyl acetate:hexane, 30:70) and dried *in vacuo*, to give white crystals of the respective esters in overall yields of 65-75%. Purity checks were done by HPLC and by the sharpness of melting points. One recrystallization from ethyl acetate or ethyl acetate-hexane mixtures with drying under nitrogen was implemented when necessary.

Solubility Determination

The solubilities of buprenorphine and its esters were obtained by equilibrating large excesses of each substance with hexane. The experiments were done at room temperature (25°C). To hasten the attainment of equilibrium, each slurry was continuously shaken in a capped test tube on a Vibrax. Samples were taken, filtered (Millex FG-13, Millipore), measured with respect to volume, and brought to dryness. The residue was reconstituted in methanol and assayed by HPLC. Binding of the compounds to the filter was checked to eliminate the possibility of drug adsorption on the filter and/or filter casing influencing the solubility determination. Sampling was repeated twice, to give three assays on each sample. Concentration versus time plots indicated that equilibrium was obtained well within 30 hours. Therefore, the equilibration times for all the studies were 30 hours.

Chromatographic Procedure

Buprenorphine and its prodrugs were assayed by HPLC using UV detection at 285 nm. A C_8 Brownlee OSS Spheri-5 micron cartridge (220 × 4.6 mm) with a guard column was used. The mobile phase consisted of 85% methanol:acetonitrile (7:3) and 15% acetate buffer pH 5. The flow rate was set at 1.5 ml/min. Standard curves exhibited excellent linearity over the entire concentration range employed in the assays.

Differential Thermal Analysis

The heats of fusion, ΔH_f, and melting points for all the drugs were determined with a Perkin-Elmer DSC 7 Differential Scanning Calorimeter. All compounds were in their crystalline free-base forms, having been freshly recrystallized from ethyl acetate or ethyl acetate-hexane mixtures and dried under nitrogen prior to performing the thermoanalytical procedure. A finely powdered, accurately weighed sample of drug (2-5 mg) was layered evenly over the bottom of an aluminum pan. Heating curves were recorded at 2.5-10°C/min. All tracings were repeated twice, for a total of three estimates. There were no appreciable differences in the thermograms for any compound from run to run.

RESULTS

The physicochemical properties of buprenorphine HCl, buprenorphine free base and six of its alkyl-ester prodrugs in free base form are summarized in Table I. All compounds exhibited only one thermal transition. The endotherm peaks correspond to the melting of the crystals. Decomposition was determined by HPLC assay of the compounds after undergoing the thermoanalytical procedure; only buprenorphine HCl decomposed rapidly upon melting. The melting

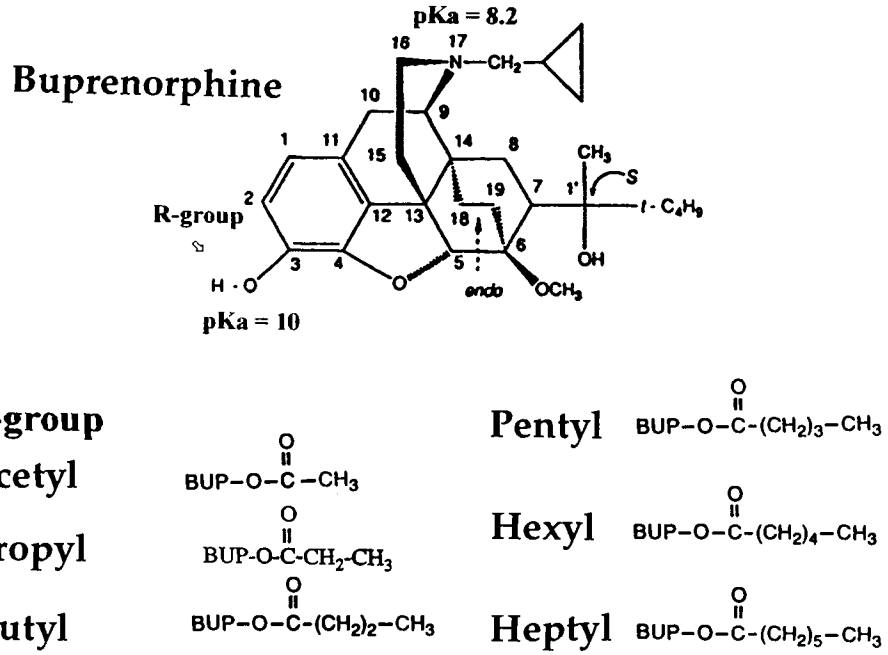

Fig. 1. Structures of buprenorphine and its alkyl esters.

points, MP, are the mean of three determinations, shown with standard error values.

Heats of fusion, ΔH_f, were calculated from the means of areas under three melting peaks, shown with standard error values. The thermodynamic activities (reference state, supercooled liquid) were calculated using equation 2 at an experimental temperature of 25°C.

The hexane solubilities for buprenorphine HCl, buprenorphine free base and six of its alkyl-ester prodrugs in free base form are summarized in Table I. These solubilities are means of at least three experiments run at 25°C and are shown with standard error values. The small magnitudes of the solubility values allowed us to set ϕ_1, the volume fraction of hexane in their saturated solutions, to unity. Using this surmise, the solubility parameters for all the solutes were calculated from equation 4. The molar volumes, V_2, needed for the calculations were estimated by the summation of the partial molal volumes of the compounds' functional groups (12). The solubility parameter of hexane, δ_1, is 14.93 $J^{1/2}cm^{-3/2}$ (13). [This value is 7.3 $cal^{1/2}cm^{-3/2}$. The conversion factor from calories to joules is 2.0455.] The experimental values for the mole fraction solubilities of the drugs in hexane, the melting points, and the heats of fusion were used in the solubility parameter calculations. These solubility parameter values are summarized in Table I, along with their respective estimated molar volumes.

DISCUSSION

The trend in melting points as a function of increasing alkyl chain length can be seen in Table I. Although there is a little irregularity in the pattern, overall the melting points

Table I. Physicochemical Properties of Buprenorphine and Its Alkyl Esters in Free Base Form

	BUP HCl	BUP Base	Acetyl	Propyl	Butyl	Pentyl	Hexyl	Heptyl
Molecular Weight (g/mol)	504	467	509	523	537	551	565	579
Melting Point °C	272.0	218.1	167.1	137.0	148.9	105.9	79.4	86.8
(st.err)	(0.7)	(0.2)	(0.2)	(0.2)	(0.3)	(0.1)	(0.8)	(0.6)
Heat of Fusion	120.9	26.8	22.4	27.1	32.4	24.0	22.6	19.3
(kJ/mol)	(10.4)	(1.4)	(0.4)	(0.2)	(1.7)	(0.9)	(0.4)	(0.2)
Activity of Solid @ 25°C	2.5×10^{-10}	0.014	0.054	0.051	0.022	0.126	0.245	0.262
Hexane Solubility Mole $\times 10^{-2}$	0.00041	0.012	1.01	0.670	0.300	1.54	3.41	3.16
(st.err.)	(.00003)	(.001)	(0.1)	(0.005)	(0.005)	(0.03)	(0.05)	(0.03)
Crystalline Density (g/ml)	not available	1.30	1.30	1.28	1.27	1.25	1.24	1.22
Molar Volume V_2 (ml/mole)	not available	359.3	392.2	407.8	424.2	440.8	457.0	473.2
Solubility Parameter δ_2, ($J^{1/2}$ $cm^{-3/2}$)	not available	20.7	18.2	18.4	18.3	18.4	18.2	18.3

decrease as the alkyl chain is extended, by over 100°C in the instances of the pentyl through heptyl esters. Other investigators who have studied alkyl chain series have also found that melting points decrease overall, but not linearly (14). The fact that all the alkyl esters exhibit lower melting points than buprenorphine base indicates that the added alkyl functionalities disrupt the intracrystalline cohesion of the drug. The enormous decreases in ester melting points relative to buprenorphine base give rise to the remarkable increases in thermodynamic activities as the alkyl chain is extended (Table I). The thermodynamic activity of the solid drug in a formulation establishes its maximum practical driving force for permeation, the saturation condition. In saying this supersaturation in a formulation is ruled out as impractical because this will eventually lead to precipitation and an unwanted change in activity.

Comparing the hexane solubilities as a function of alkyl chain length in Table I, it can be seen that four of the compounds are over one-hundred times more soluble in hexane than buprenorphine base. The changes in hexane solubilities of the esters mirror the changes in crystallinity seen through the melting points.

Figure 2 shows a plot of thermodynamic activity as a function of mole fraction hexane solubility for buprenorphine and its alkyl esters, including the value for the isobutyric acid derivative which will otherwise be reported on separately. The correlation coefficient for the line in this plot is 0.98. Amongst other things, this relationship tells us that one can confidently predict the hexane solubility of a new member of this series following its thermoanalytical characterization.

According to Table I, an increase in alkyl chain length had no measurable effect on the solubility parameters of the esters. Rather, the values are equivalent and thus the cohesive energy densities, the squares of these values, are also equivalent. The net result is that levels of non-ideality are comparable from one compound to the next. The significant difference between the solubility parameters of the esters and buprenorphine base does tell us that esterification decreases the cohesion energy per unit volume. This decrease in intracrystalline cohesive energy is reflected in the decreased melting points and increased hexane solubilities of the esters. But this is not the whole story, for packing and orientation in the crystal also affect the level of bonding in this state. It is differences in the latter which most determine the physical expressions of the esters.

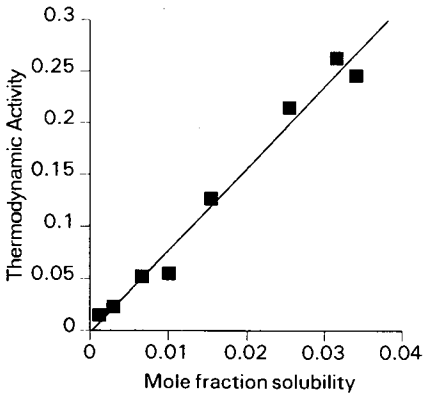

Fig. 2. A plot of thermodynamic activity as a function of mole fraction hexane solubility for buprenorphine and its alkyl esters. The correlation coefficient for this line is 0.98.

In conclusion, one can clearly see that the modification of buprenorphine with an alkyl-ester moiety accomplishes the physicochemical task required to improve its flux across a lipoidal membrane, as long as the diffusion coefficient of the drug has not been decreased and the molecular mechanism of permeation remains the same. We view the compounds as potential prodrugs for buprenorphine and have studies underway on their relative permeabilities through skin.

ACKNOWLEDGMENTS

This work was supported by NIDA Grant DA-07575 and the Upjohn Research Endowment Fund. ALS was supported by The University of Michigan's Regents' Fellowship and the Lilly Endowment Fellowship. Part of this work was presented at The Eighth Annual American Association of Pharmaceutical Scientists Meeting, Orlando, Florida, November 1993.

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