International Journal of Pharmaceutics, 18 (1984) 149–156
Elsevier

IJP 00620

The relationship between intrinsic dissolution rates and solubilities in the water–ethanol binary solvent system

Martin Nicklasson and Arne Brodin

Research and Development Laboratories, Pharmaceutics, Astra Läkemedel AB, S-151 85 Södertälje (Sweden)

(Received March 24th, 1983)
(Modified version received August 15th, 1983)
(Accepted August 2nd, 1983)

Summary

Solubilities and intrinsic dissolution rates for alaproclate hydrochloride, oxazepam and dextropropoxyphene napsylate have been determined in binary mixtures of water and ethanol. On a log-log scale, a linear relationship between the solubilities and the corresponding intrinsic dissolution rates with a slope of 1.0 was found. A solubility range of four log-units was covered. However, dextropropoxyphene napsylate in pure ethanol appeared to diverge from this relationship. This was explained by a change in crystalline form as indicated by differential scanning calorimetry. By calculating the solubility in ethanol before the crystal form changed, a better fit for the solubility–intrinsic dissolution rate relationship was obtained.

Introduction

Solubilities of drug compounds in various aqueous–non-aqueous solvent systems have been shown great interest (Andersson et al., 1980; Flynn et al., 1979; Fung and Higuchi, 1971; Martin et al., 1980; Martin and Miralles, 1982). A new approach to predict drug solubilities in binary polar mixtures using a modified Hildebrand solubility equation has recently been demonstrated (Martin et al., 1980; Martin and Miralles, 1982). Various explanations for the solubility behavior of different com-

Correspondence: M. Nicklasson, Research and Development Laboratories, Pharmaceutics, Astra Läkemedel AB, S-151 85 Södertälje, Sweden.

pounds in non-aqueous solvents such as hydrogen-donating and hydrogen-accepting abilities of solute and solvent, specific solvation or solvate complexes and steric factors have thus been discussed.

Dissolution rates of cholesterol have been shown to be directly related to the measured solubilities in organic solvents (Flynn et al., 1979). Direct relationships between solubilities and intrinsic dissolution rates for various substances in aqueous buffer solutions have also been reported (Parrott et al., 1955; Hamlin et al., 1965; Nelson and Shah, 1975; Nicklasson et al., 1981).

During the preformulation stage, an extensive understanding of the solubility behavior in vitro of a new drug compound in various solvent systems is desirable. At this stage of the formulation work, a very small quantity of the drug compound is available for conventional solubility experiments. However, by using a rotating disk method to determine the intrinsic rate of dissolution, information about the corresponding solubility can be obtained from a limited drug quantity (about 1.0 g) by applying the direct relationship between the two properties mentioned above.

In the early formulation of solid preparation it is necessary to have a working in vitro dissolution method. For less soluble drugs it might be preferable to use solvent mixtures instead of increasing the aqueous sink volume. Also here, the knowledge of a substance dissolution behavior is of interest.

The aim of the present paper was to assess whether the direct relationship between solubilities and intrinsic dissolution rates found in water also exists in the water–ethanol mixture system.

Experimental

Chemicals

Alaproclate hydrochloride (Astra Läkemedel AB, Sweden), oxazepam (Profarmaco, Italy), and dextropropoxyphene napsylate (Eli Lilly, U.K.) were used as test compounds. Distilled water and ethanol 99.5% w/w of pharmaceutical grade were used as solvents.

Intrinsic rates of dissolution

The different substances were compressed into disks in an excenter press by hand. The preparation of the disks has been described previously (Nicklasson et al., 1981). The disks were attached eccentrically on a round rotating support with the dissolving surface area (0.50 cm^2) downward. The distance from the center of the rotating support to the outermost edge of the dissolving surface was 16 mm. The dissolution rate was calculated by linear regression analysis from the amount dissolved per cm^2 vs time linear relationship. One disk at each rotation speed (200, 300, 400 and 500 rpm) was used. The intrinsic dissolution rate at infinite speed of rotation was calculated by an extrapolation procedure (Nicklasson et al., 1983). Distilled water, ethanol and binary mixtures of them such as 25/75, 50/50 and 75/25 v/v were used as dissolution media. The dissolution experiments were performed at 22°C and the sink volume was 50.0 ml. At each run, the dissolution media was continuously

recirculated via a peristaltic pump through a flow cell in a spectrophotometer (Pye-Unicam SP 8-100).

Solubilities

Drug in excess of the saturation concentration was added to the solvents and solvent mixtures. The suspensions were equilibrated at 22°C for 18–24 h using a magnetic stirrer. Two aliquots of the suspensions were filtered through 0.1 μm polycarbonate filters (Nucleopore) and then diluted to suitable concentrations for spectrophotometry.

For dextropropoxyphene napsylate, another experiment procedure was also applied. Samples were taken after 1, 5, 10 and 30 min and the amount dissolved was determined as previously described.

Differential scanning calorimetry

Crystals of dextropropoxyphene napsylate equilibrated with ethanol for 20 h were collected and allowed to dry overnight at room temperature. Samples of 15 mg were placed in a 910 Differential Scanning Calorimeter (Du Pont Instruments). Thermograms were also recorded for dextropropoxyphene napsylate crystals which had not been in contact with ethanol.

Results and Discussion

When mounting a disk horizontally on the rotating support, laminar flow past the disk surface may be assumed (Levich, 1962; Riddiford, 1966; Grijseels et al., 1981). At this hydrodynamic condition, an equation describing the dissolution rate as a function of the angular velocity and the distance from the axis of the support has been found (Nicklasson et al., 1982),

$$G = k_1 - \frac{k'}{R\sqrt{\omega}} \tag{1}$$

where G = observed dissolution rate ($mg \cdot cm^{-2} \cdot s^{-1}$), k_1 = intrinsic dissolution rate ($mg \cdot cm^{-2} \cdot s^{-1}$), k' = proportionality constant, R = distance from the disk to the axis of the rotating support (cm) and ω = angular velocity (s^{-1}).

By plotting the observed dissolution rates (G) as a function of $1/(R\sqrt{\omega})$ and then extrapolating to $1/(R\sqrt{\omega}) = 0$, k_1 is obtained. Fig. 1 shows the relationship between G and $1/(R\sqrt{\omega})$ for alaproclate hydrochloride in different water–ethanol mixtures indicating the validity of Eqn. 1. The intrinsic rates of dissolution for alaproclate hydrochloride, i.e. the intersections with the y-axis, increase with increasing ethanol concentration.

The individual solubilities and intrinsic dissolution rates for the 3 compounds studied are summarized in Table 1. The changes in the intrinsic dissolution rates with increasing ethanol concentration are closely related to the changes in the solubilities. Previously reported data have also indicated a good correlation between

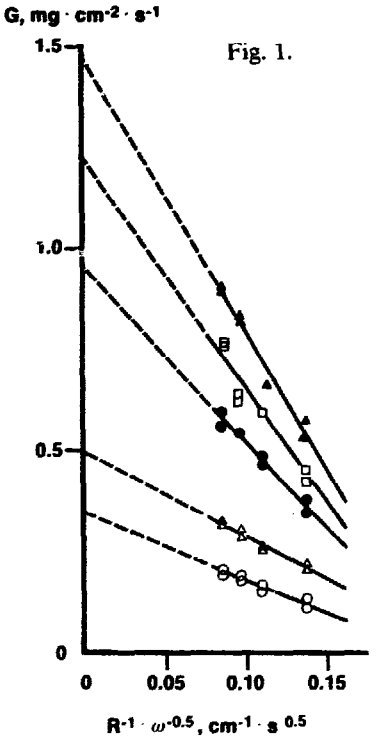

Fig. 1.

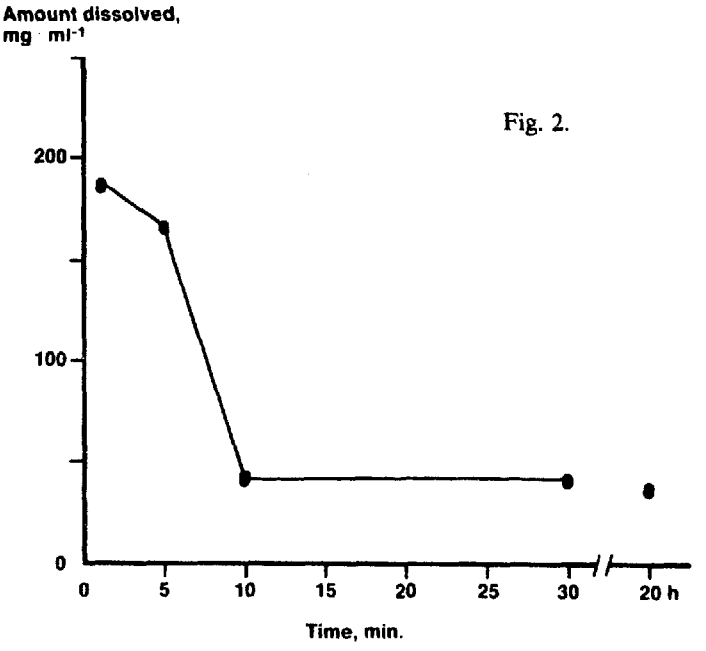

Fig. 2.

Fig. 1. Observed dissolution rates for alaproclate hydrochloride as a function of angular velocity and distance from the axis of the rotating support according to Eqn. 1. ○, water; △, ethanol/water 25/75 v/v; ●, ethanol/water 50/50 v/v; □, ethanol/water 75/25 v/v; ▲, ethanol.

Fig. 2. Amount dissolved as a function of time for dextropropoxyphene napsylate in ethanol (22°C).

TABLE 1

SOLUBILITIES (S, n = 2) AND INTRINSIC DISSOLUTION RATES ($k_1 \pm$S.E., df = 6) FOR ALAPROCLATE HYDROCHLORIDE (Ala), DEXTROPROPOXYPHENE NAPSYLATE (DPOP naps.) AND OXAZEPAM (Oxa) IN VARIOUS MIXTURES OF WATER AND ETHANOL AT 22°C.

Water/ethanol	S (mg/ml)			$k_1 \times 10^2$ (mg·cm^{-2}·s^{-1})		
% v/v	Ala	DPOP naps.	Oxa	Ala	DPOP naps.	Oxa
100/0	31, 31	1.4, 1.4	0.02, 0.02	34 ± 1.1	0.7 ± 0.05	0.01 ± 0.002
75/25	96, 95	3.4, 3.4	0.09, 0.09	49 ± 3.0	1.2 ± 0.10	0.06 ± 0.007
50/50	225, 226	33, 33	1.2, 1.3	94 ± 8.5 **	9.6 ± 0.39	0.47 ± 0.036
25/75	269, 267	104, 103	4.0, 4.1	120 ± 4.6 **	32 ± 2.4	1.9 ± 0.11
0/100	310, 310	38, 38 185, 183 *	3.4, 3.4	146 ± 8.0 **	43 ± 2.9	1.8 ± 0.07

* After 1 min, c.f. Fig. 2.
** df = 5.

intrinsic dissolution rates and aqueous solubilities of different substances (Hamlin et al., 1965; Nelson and Shah, 1975; Nicklasson et al., 1981). Further, solubilities of cholesterol in organic solvents were found to be directly related to dissolution rates determined with a rotating disk method (Flynn et al., 1979). In the present work, one deviation from this relationship was found: dextropropoxyphene napsylate in pure ethanol. The intrinsic dissolution rate for dextropropoxyphene napsylate increases with increasing ethanol concentration as shown in Table 1. However, the corresponding solubility after 20 h decreases drastically in pure ethanol compared to the solubility in 75% v/v of ethanol. To explain the deviation of dextropropoxyphene napsylate, its solubility in pure ethanol was reinvestigated. When equilibrating an excess amount of dextropropoxyphene napsylate for 20 h at 22°C, the solubility was determined to 38 mg/ml. Using a more moderate amount of substance corresponding to a theoretical solubility of about 50 mg/ml, a clear solution was obtained. However, after about 10 min, a sudden precipitation was observed. The suspension was allowed to equilibrate for 20 h after which the solubility was confirmed to be 38 mg/ml. The time dependence of the amount dissolved using a large excess of substance is shown in Fig. 2. The change in solubility seems to take place within the first 10 min. The solubilities of the 3 crystalline forms of prednisolone behave similarly (Wurster and Taylor, 1965). The anhydrous form A was rapidly converted to the hydrate form. A solubility maximum obtained within less than 1 h was not considered as the true solubility but only as reflecting a steady-state between dissolution of the anhydrous form and subsequent crystallization of the hydrate. In a recently published paper (Fokkens et al., 1983), it was shown that theophyllin

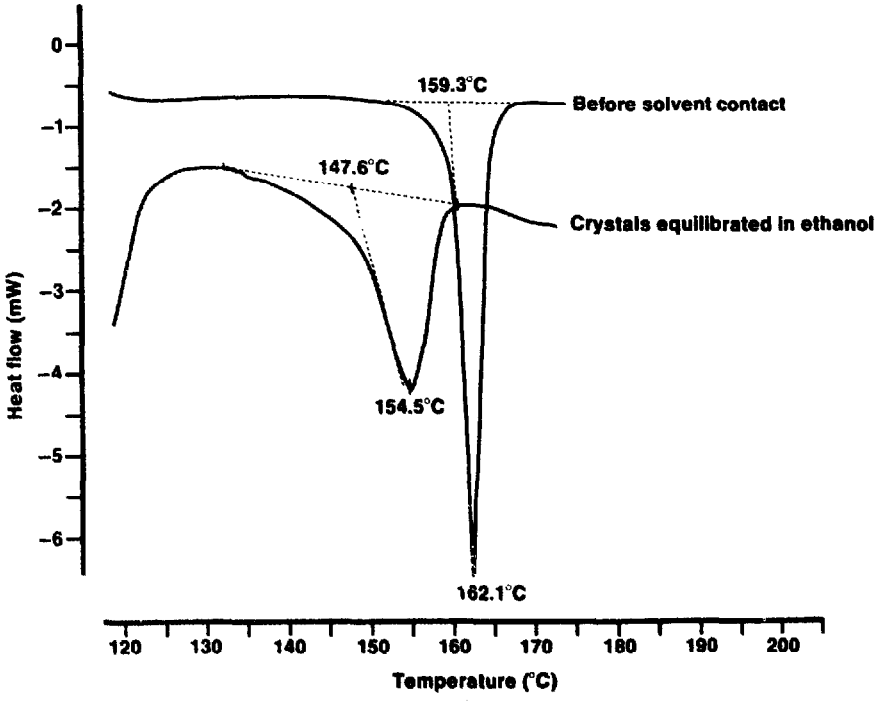

Fig. 3. Differential scanning calorimetry of dextropropoxyphene napsylate (15 mg, 5°C/min).

crystallizes in contact with water forming a pseudo-polymorph, a hydrate which is less soluble than crystalline theophylline. This transition did only take place below a given temperature. If the temperature was higher than the transition temperature, the solubility was found to be dependent on the pre-treatment of the drug. Phenobarbital also transforms from one modification to another in water with a decrease in solubility (Eriksson, 1961).

When plotting the solubilities as a function of intrinsic dissolution rates on a log-log scale for dextropropoxyphene napsylate excluding the ethanol value, the following regression line was calculated: $\log S = 1.12(\pm 0.055) \log k_1 + 2.62(\pm 0.085)$, $r = 0.998$. By using the k_1-value for dextropropoxyphene napsylate determined in pure ethanol (0.43 $mg \cdot cm^{-2} \cdot s^{-1}$) the corresponding ethanol solubility was calculated by extrapolation to 162 ± 31 mg/ml ($\pm$S.E.). This value is close to the experimental one of 185 mg/ml determined after 1 min (see Fig. 2).

In Fig. 3, thermograms are shown for dextropropoxyphene napsylate crystals

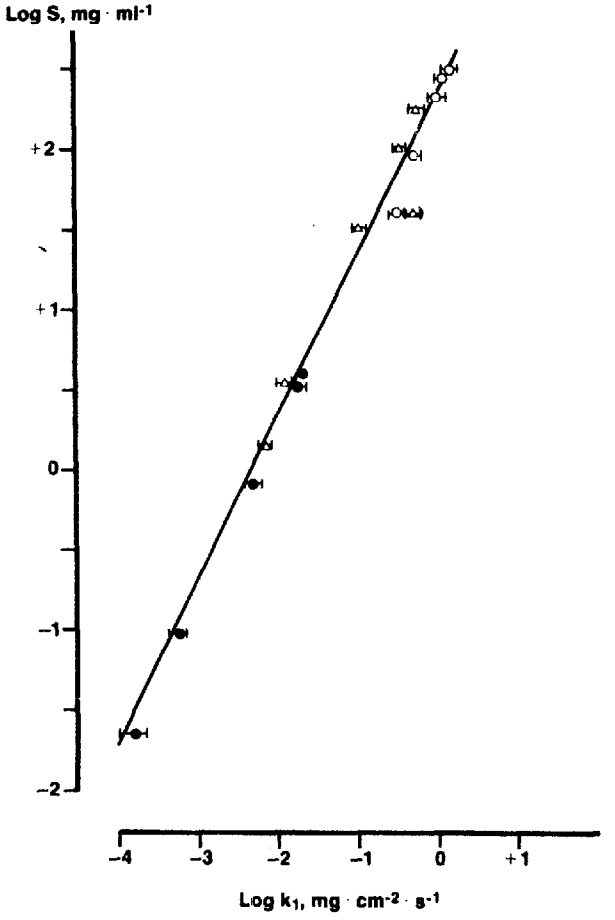

Fig. 4. Relationship between solubility and intrinsic rate of dissolution for different substances in the water–ethanol binary system. The symbol within paranthesis denotes the solubility data obtained for dextropropoxyphene napsylate in ethanol after 20 h. Bars represent 95% confidence intervals. ○, alaproclate hydrochloride; △, dextropropoxyphene napsylate; ●, oxazepam.

before solvent contact, i.e. as obtained, and after equilibration in ethanol followed by drying overnight. The difference in the thermograms clearly indicates a change in crystalline form when the compound is dissolved in ethanol. An ethanol solvate may form. A similar solubility phenomenon has also been demonstrated for cholesterol dissolved in various *n*-alkanols (Flynn et al., 1979). As pointed out by the same authors, a general caution to solubility analysis has to be observed due to the remarkable sensitivity of some compounds to the solvents used.

Fig. 4 shows the relationship obtained between solubilities and intrinsic dissolution rates for all substances and solvent combinations tested. The plot covers a solubility range of 4 log-units. The regression line is $\log S = 0.99(\pm 0.037) \log k_1 + 2.27(\pm 0.064)$, $n = 16$, $r = 0.990$. At the calculation of the regression line, the solubility value determined after 1 min in ethanol is used for dextropropoxyphene napsylate. For comparison, the dextropropoxyphene solubility obtained after 20 h is also plotted.

It has previously been demonstrated that the k_1-values obtained from vertically mounted rotating disks were equivalent to the k_1-values obtained by using the same way of mounting as described in this paper (Nicklasson et al., 1982). The slope and intercept with 95% confidence intervals obtained from the relationship between log S and log k_1 for vertically mounted disks in aqueous buffer solution at 37°C were 1.0 ± 0.30 and 1.94 ± 0.33, respectively, $n = 4$. In spite of the difference in temperature there is obviously no statistical difference between the two regression lines, ($P = 0.05$). However, compensating for the temperatures makes the difference in intercept even smaller. This means that the same relationship exists between solubilities and intrinsic dissolution rates with both the water and the water–ethanol system.

Conclusion

On a log-log scale, a linear relationship with a slope = 1 was found between intrinsic dissolution rates and solubilities of alaproclate hydrochloride, oxazepam and dextropropoxyphene napsylate in various water–ethanol mixtures. The results were in good agreement with previously published data on dissolution rates and solubilities in water.

One apparent deviation from this relationship was observed. For dextropropoxyphene napsylate in ethanol, a much lower solubility than expected from the intrinsic dissolution rate measurement was found. Differential scanning calorimetry data indicated a change in crystalline form when dextropropoxyphene napsylate was dissolved in ethanol. However, by using the amount dissolved after only 1 min, a better fit for the solubility–intrinsic dissolution rate relationship was obtained.

Acknowledgement

We wish to thank Mrs. Louise Silwer for skillful technical assistance.

References

Andersson, B.D., Rytting, J.H. and Higuchi, T., Solubility of polar organic solutes in nonaqueous systems: role of specific interactions. J. Pharm. Sci., 69 (1980) 676–680.

Eriksson, S.O., The solubility of phenobarbitone. Svensk Farm. Tidskr., 65 (1961) 353–359.

Flynn, G.L., Shah, Y., Prakongpan, S., Kwan, K.H., Higuchi, W.I. and Hofman, A.F., Cholesterol solubility in organic solvents. J. Pharm. Sci., 68 (1979) 1090–1097.

Fokkens, J.G., von Amelsfoort, J.G.M., de Blaey, C.J., de Kruif, C.G. and Wilting, J., A thermodynamic study of the solubility of theophylline and its hydrate. Int. J. Pharm., 14 (1983) 79–93.

Fung, H.L. and Higuchi, T., Molecular interactions and solubility of polar nonelectrolytes in nonpolar solvents. J. Pharm. Sci., 60 (1971) 1782–1788.

Grijseels, H., Crommelin, D.J.A. and de Blaey, C.J., Hydrodynamic approach to dissolution rate. Pharm. Weekbl. , 3 (1981) 129–144.

Hamlin, W.E., Northam, J.I. and Wagner, J.G., Relationship between in vitro dissolution rates and solubilities of numerous compounds representative of various chemical species. J. Pharm. Sci., 54 (1965) 1651–1653.

Levich, V.G., Physicochemical Hydrodynamics, Prentice-Hall, Englewood Cliffs, NJ, 1962, p. 1.

Martin, A., Newburger, J. and Adjei, A., Extended Hildebrand solubility approach: solubility of theophylline in polar binary solvents. J. Pharm. Sci., 69 (1980) 487–491.

Martin, A. and Miralles, M.J., Extended Hildebrand solubility approach: solubility of tolbutamide, acetohexamide, and sulfisomidine in binary solvent mixtures. J. Pharm. Sci., 71 (1982) 439–442.

Nelson, K.G. and Shah, A.C., Convective diffusion model for a transport-controlled dissolution rate process. J. Pharm. Sci., 64 (1975) 610–614.

Nicklasson, M., Brodin, A. and Nyqvist, H., Studies on the relationship between solubility and intrinsic rate of dissolution as a function of pH. Acta Pharm. Suec., 18 (1981) 119–128.

Nicklasson, M., Brodin, A. and Sundelöf, L.-O., On the determination of true intrinsic rates of dissolution by means of a generalized rotating disk method. Acta Pharm. Suec., 19 (1982) 109–118.

Nicklasson, M., Brodin, A. and Sundelöf, L.-O., On the determination of true dissolution rate parameters from rotating disc experiments. Int. J. Pharm., 15 (1983) 87–95.

Parrott, E.L., Wurster, D.E. and Higuchi, T., Investigation of drug release from solids I: Some factors influencing the dissolution rate. J. Am. Pharm. Assoc., 44 (1955) 269–273.

Riddiford, A.C., In P. Delahay (Ed.), Advances in Electrochemistry and Electrochemical Engineering, Interscience Publishers, New York, 1966, pp. 47–116.

Wurster, D.E. and Taylor, P.W., Dissolution kinetics of certain crystalline forms of prednisolone. J. Pharm. Sci , 54 (1965) 670–676.