J. Pharm. Pharmacol. 1987, 39: 587–591
Received December 8, 1986

Common ion effect on solubility and dissolution rate of the sodium salt of an organic acid

ABU T. M. SERAJUDDIN*, PAI-CHANG SHEEN AND MATTHEW A. AUGUSTINE

Rorer Central Research, 800 Business Center Drive, Horsham, PA 19044, USA

The solubility and the dissolution rate of the sodium salt of an acidic drug (REV 3164; 7-chloro-5-propyl-1*H*,4*H*-[1,2,4]triazolo[4,3-*a*]quinoxaline-1,4-dione) decreased by the effect of common ion present in aqueous media. The solubility of the sodium salt of REV 3164 in a buffered medium was much lower than that in an unbuffered medium. Also, the presence of NaCl decreased its solubility in water. The apparent solubility product (K'_{sp}) of the salt, however, did not remain constant when the concentration of NaCl was changed. A decrease in K'_{sp} value with the increase in NaCl concentration was observed; for example, the K'_{sp} values at 0 and 1 M NaCl were $7{\cdot}84 \times 10^{-4}$ and $3{\cdot}94 \times 10^{-4}$ M^2, respectively. Even when corrected for the effect of ionic strength, the solubility product decreased. This decrease in the solubility product in the presence of NaCl indicated a decrease in the degree of self-association (increase in activity coefficient) of the drug in aqueous media.

Various inorganic and organic salts are often used in the preparation of media for the dissolution study of solid drugs, as buffering agents, and in adjusting osmotic pressure of parenteral and ophthalmic solutions. They may also be present as excipients and preservatives in solid and liquid dosage forms. These added ions may influence the solubility (Chowhan 1978) and the dissolution rate (Serajuddin & Rosoff 1984) of the salt forms of drugs by the common ion effect.

In recent years several investigators observed that the aqueous solubilities of the salts of acidic drugs varied depending on the cation or the base used to prepare the salts (Chowhan 1978; Anderson & Conradi 1985). The solubility products (K_{sp}) of the salts of an acidic drug with different cations were also different (Chowhan 1978; Anderson & Conradi 1985). No systematic study was undertaken, however, to determine the effects of a change in concentration of common ions on the solubility and the dissolution rate of the salt forms of organic acids. During the preformulation study of an antiallergic drug, REV 3164 (7-chloro-5-propyl-1*H*,4*H*[1,2,4]-triazolo[4,3-*a*]quinoxaline-1,4-dione), we determined the pH-solubility profiles of its acid and sodium salt forms (see Khandwala et al 1984; Liebowitz et al 1984 for its biochemical and pharmacological activities). Since the ions present in the buffered solutions appeared to lower the aqueous solubility of the sodium salt, we investigated the effect of varying the concentration of common ion (Na^+) on the solubility and on the dissolution rate of the sodium salt. The results are presented herein. Based on solubility data, the possible effect of electrolytes on the self-association of drugs is also discussed.

* Correspondence and present address: The Squibb Institute for Medical Research, Pharmaceutical R&D Department, New Brunswick, New Jersey 08903, USA.

MATERIALS AND METHODS

Chemicals

The compound, REV 3164 (m.w. 278·7), and its sodium salt were synthesized by the Medicinal Chemistry Department of Revlon Health Care Group, Tuckahoe, NY. The purity of the materials used was >99·5%. All other reagents and chemicals used were of analytical grade or better.

Equilibrium solubility

The equilibrium solubilities of REV 3164 and its sodium salt in buffers of various pH and in sodium chloride solutions were determined at 25 °C. An excess of drug was shaken (Burrell Wrist Action Shaker) with ~10 mL of each medium in a 25 mL volumetric flask for 18–24 h. The temperature (25 °C) was maintained constant by suspending the flasks in a water bath. The buffers at pH 1·2 to 9 were prepared according to the United States Pharmacopeia XIX. The sodium carbonate-bicarbonate buffers (Scientific Tables 1970) were used at pH 9–11. The NaCl solutions were prepared using deionized water.

The solubilities of the sodium salt of REV 3164 were also determined in unbuffered media by adjusting the pH values with either HCl or NaOH solutions. The solutions were equilibrated for ~6 h

after each adjustment of pH; preliminary studies showed that the solubility did not change if the equilibration was continued for 24 h.

The pH values of the solutions were recorded after equilibration, and aliquots were filtered through Millipore 0·45 μm filters and analysed spectrophotometrically. There was no significant adsorption of the drug to the filter nor was there any degradation of the compound after 24 h in the various pH ranges used.

pK_a

Solutions of REV 3164 in water (5 μg mL^{-1}) at different pH values were prepared by the addition of dilute HCl or NaOH. Ultraviolet spectra of these solutions were recorded, and the apparent pK_a was calculated (Connors 1975) at 264 nm where the greatest difference in the absorbance values of ionized and un-ionized species of REV 3164 was observed.

Intrinsic dissolution rate

Dissolution rates of the sodium salt of REV 3164 in various media at 25 °C from a constant surface area of 0·95 cm^2 were determined by using the apparatus designed by Wood et al (1965). 300 mL of each medium were used, and the apparatus was rotated at 180 rev min^{-1}. The experimental conditions were described earlier (Serajuddin & Jarowski 1985).

Analysis of drug

Aliquots of solutions collected during solubility and dissolution studies were analysed spectrophotometrically at the wavelength of 314 nm after suitable dilution with acidified methanol (1 M HCl : CH_3OH, 1 : 9). The addition of HCl solution to methanol ensured the existence of drug in solution as an un-ionized species, so that there was no variation in the absorbance of drug due to possible ionization at a high pH.

RESULTS AND DISCUSSION

pH-solubility profile and pK_a

The pH-solubility profiles of the acid form of REV 3164 in buffered media and of its sodium salt in both buffered and unbuffered media are shown in Fig. 1. The pH-solubility profiles of REV 3164 and its sodium salt were similar in the pH range of 1·1 and 9·6; the solubility profiles of the sodium salt in buffered and unbuffered media in this pH range were also identical. At pH > 9·6, however, a great difference in the solubility profiles in buffered and unbuffered media was observed. The apparent pK_a value calculated from the UV spectral change was 7·57. A theoretical solubility profile (Chowhan 1978) calculated at pH < 9·6 by using this pK_a value and the solubility of the un-ionized drug as 0·007 mg mL^{-1} fitted the data points. This indicated there was good agreement between the pK_a value and the solubility data.

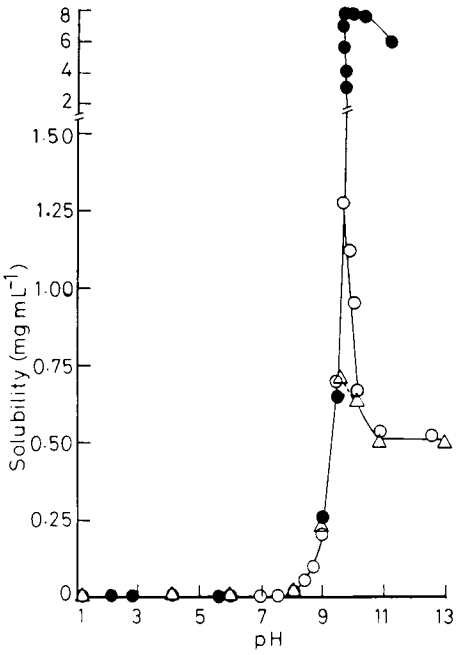

FIG. 1. pH-solubility profiles of REV 3164 in buffered media (○) and of its sodium salt in buffered (△) and unbuffered (●) media at 25 °C.

It has been reported that a pH of maximum solubility (pH_{max}) exists in the pH-solubility profile of an organic acid and its sodium salt (Chowhan 1978; Serajuddin & Jarowski 1985). At pH > pH_{max}, a solution is saturated with respect to the ionized or salt form of the acid, i.e. the solid phase in equilibrium with a saturated solution is the salt. In contrast, a solution at pH < pH_{max} is saturated with un-ionized species (acid). The pH_{max} is, therefore, the intersection of the solubility profiles in equilibrium with salt and acid forms. For REV 3164 and its sodium salt, the observed pH_{max} in both buffered and unbuffered media was between 9·6 and 9·8. Elemental analysis confirmed that the solid phases in equilibrium with solutions at pH lower and higher than the pH_{max} were REV 3164 and its sodium salt, respectively. It was also observed in preliminary experiments that the pH_{max} value decreased below 9·6 if the solubility of the sodium salt was lowered

by the addition of sodium chloride because the solubility profiles of the acid and the salt intersected at a lower pH.

Common ion effect on the solubility of the sodium salt

Since, as mentioned above, the residual solid phase at pH > pH_{max} is in the salt form, the chemical equilibrium constant (K) of a saturated solution at such a pH may be expressed as:

$$K = \frac{[Na^+]\,[A^-]s}{(NaA)_{solid}} \quad (1)$$

where Na^+, A^- and NaA represent sodium ion, ionized acid and salt, respectively, and s represents the saturation species. Therefore, the apparent solubility product (K'_{sp}) at such a pH would be:

$$K'_{sp} = [Na^+]\,[A^-]_s \quad (2)$$

Correcting for the activity, eqn 2 may be written as:

$$K^\circ_{sp} = [Na^+]\,[A^-]_s\,\gamma_+\,\gamma_- \quad (3)$$

where K°_{sp} is the theoretical solubility product (corrected for activity), and γ_+ and γ_- are the activity coefficients for positively and negatively charged ions, respectively.

The effect of common ion (Na^+) on the solubility of the sodium salt of REV 3164 in water at 25 °C is shown in Table 1. The pH values of the solutions were higher than the pH_{max}. Since the concentration of the un-ionized species of drug at such a pH was minimal, [A^-] was considered equal to the total solubility, S_T. A direct measurement of the activities of Na^+ and A^- was beyond the scope of the present study, and may not always be possible; therefore, the K°_{sp} values were not determined. We could, however, correct the values of the solubility products for the ionic strength effect by using the literature values for the activity coefficients of sodium ion (γ_+) (Niebergall 1980), and by theoretically calculating the activity coefficient of the ionized drug (Martin et al 1983). Similar correction in the calculation of the solubility product of organic salts was also made by other investigators (Anderson & Conradi 1985). The apparent solubility product (K'_{sp}) and the solubility product corrected for the effect of ionic strength (K''_{sp}) are given in Table 1. Since no consideration for any possible self-association of drug was made in calculating the activity coefficients of the drug (γ_-), the values of γ_- given in Table 1 may be different from their real values. As a result, the solubility product calculated by correcting for the effect of ionic strength only (K''_{sp}) may not represent the true solubility product (K°_{sp}). The data presented in Table 1 also lead to this conclusion. The K'_{sp} values decreased with the increase in NaCl concentration. If corrected for the activities of the species involved, the solubility product should remain constant. However, as shown in Table 1, it decreased with an increase in NaCl concentration even when the correction for the effect of the ionic strength was made. Moreover, it appears that the magnitude of the decrease was greater when they were corrected for the 'activities'; for an increase in NaCl concentration from 0 to 1 M, the decrease in K'_{sp} and K''_{sp} were 2·8 and 5·3-fold, respectively. Thus, some factors other than the ionic strength may be responsible for the observed decrease in the solubility product.

Mechanism of the decrease in solubility product

The apparent solubility products (K'_{sp}) of the hydrochloride salts of organic bases were reported to

Table 1. Effect of sodium chloride concentration on total solubility (S_T) and solubility product (K_{sp}) of the sodium salt of REV 3164 in water at 25 °C.

	S_T			Activity coefficients			
[NaCl], M	mg mL^{-1}	M	[Na^+], M	γ_-	γ_+	K'_{sp}, M^2	K''_{sp}, M^2
0	7·80 ± 0·20[a]	0·0280	0·0280[b]	0·845[c]	0·850[d]	$7{\cdot}84 \times 10^{-4}$[e]	$5{\cdot}62 + 10^{-4}$[f]
0·01	6·06 ± 0·18	0·0217	0·0317	0·837		$6{\cdot}88 \times 10^{-4}$	$4{\cdot}90 \times 10^{-4}$
0·02	4·28 ± 0·54	0·0154	0·0354	0·830		$5{\cdot}45 \times 10^{-4}$	$3{\cdot}85 \times 10^{-4}$
0·03	3·33 ± 0·03	0·0119	0·0419	0·819		$4{\cdot}99 \times 10^{-4}$	$3{\cdot}60 \times 10^{-4}$
0·04	2·68 ± 0·07	0·0096	0·0496	0·807		$4{\cdot}76 \times 10^{-4}$	$3{\cdot}25 \times 10^{-4}$
0·05	2·20 ± 0·04	0·0079	0·0579	0·796	0·823	$4{\cdot}57 \times 10^{-4}$	$3{\cdot}01 \times 10^{-4}$
0·10	1·06 ± 0·09	0·0038	0·1038	0·751	0·780	$3{\cdot}94 \times 10^{-4}$	$2{\cdot}35 \times 10^{-4}$
0·20	0·50 ± 0·02	0·0018	0·2018	0·694	0·730	$3{\cdot}63 \times 10^{-4}$	$1{\cdot}77 \times 10^{-4}$
0·50	0·17 ± 0·00	0·00061	0·5006	0·615	0·68	$3{\cdot}05 \times 10^{-4}$	$1{\cdot}29 \times 10^{-4}$
1·00	0·078 ± 0·002	0·00028	1·0003	0·556	0·66	$2{\cdot}80 \times 10^{-4}$	$1{\cdot}06 \times 10^{-4}$

[a] Average ± s.d. of three determinations. [b] Calculated by adding the concentration of NaCl to the concentration of drug. [c] Calculated according to (Martin et al 1983): $\log \gamma_- = -[(Az_+z_-\sqrt{\mu})/(1 + \sqrt{\mu})]$, where z is the valence or charge of the ionic species, μ is the ionic strength, and A is a constant (0·51 at 25 °C). [d] From Niebergall (1980). A value of 0·850 was used for NaCl concentrations of 0 to 0·04 M. [e] Calculated according to eqn 2. [f] Calculated according to eqn 3.

decrease when the chloride ion was added in the forms of NaCl or HCl (Bogardus & Blackwood 1979; Serajuddin & Mufson 1985). The K'_{sp} values of a dye, thionine hydrochloride, also decreased in the presence of NaCl (Haugen & Hardwick 1963). For example, the K'_{sp} value of doxycycline hydrochloride decreased from $5{\cdot}3 \times 10^{-3}$ to $2{\cdot}7 \times 10^{-3}$ M^2 when 0·15 M NaCl was added; it decreased to $2{\cdot}1 \times 10^{-3}$ M^2 at 0·35 M NaCl, with no further change at higher NaCl concentration (Bogardus & Blackwood 1979). The decrease was more dramatic in the case of thionine hydrochloride (Haugen & Hardwick 1963). From an initial value of $6{\cdot}2 \times 10^{-4}$ M^2 in water, K'_{sp} decreased to a limiting value of $1{\cdot}2 \times 10^{-5}$ M^2 in the presence of ~0·2 M NaCl. Such decreases in K'_{sp} were explained on the basis of the self-association of organic molecules (Haugen & Hardwick 1963; Bogardus & Blackwood 1979). Many drugs are known to form self-associated complexes in aqueous solutions (Attwood & Florence 1983; Thoma & Albert 1983). The self-association would cause the total solubility to be higher than the activity of the drug in solution. Thus, the apparent solubility product (K'_{sp}) calculated on the basis of such solubility data would be higher than the real value (K°_{sp}). It was suggested that the degree of self-association decreases with the increase in common ion concentration (Haugen & Hardwick 1963; Bogardus & Blackwood 1979). This would reduce the difference between the solubility and the activity of the compound and, as a result, the apparent solubility product would decrease to a value closer to K°_{sp}.

The data presented in Table 1 may also be explained on the basis of the above mechanism. The decrease in K'_{sp} suggests a decrease in self-association and the consequent increase in the activity coefficient of the drug in the presence of NaCl. This effect is in agreement with the recent observation by Strykowski & Pandit (1986) that the octanol : water partition coefficient of the sodium salt of an acidic drug increases in the presence of NaCl. The authors explained their results by suggesting that NaCl promoted ion-pair formation in the organic phase; however, it is also possible that the higher partition coefficient could be due to lower self-association (increased activity) of the drug in the aqueous phase.

Whether the added electrolyte would decrease or increase the degree of self-association of drugs may depend on the nature of the drug and the type of aggregates formed. Many drugs like REV 3164 contain rigid ring structures and do not have any particular polar or non-polar end; the hydrophobicity on both sides of each flat or nearly flat structure is almost symmetrical. As a result, the molecules undergo 'stacking'-type aggregation (Mukerjee 1973). If ionized groups are attached to the planar ring systems, these groups are radially distributed and do not prevent the face-to-face association of the molecules. This type of aggregate is stabilized in aqueous solutions by the hydration of the hydro-

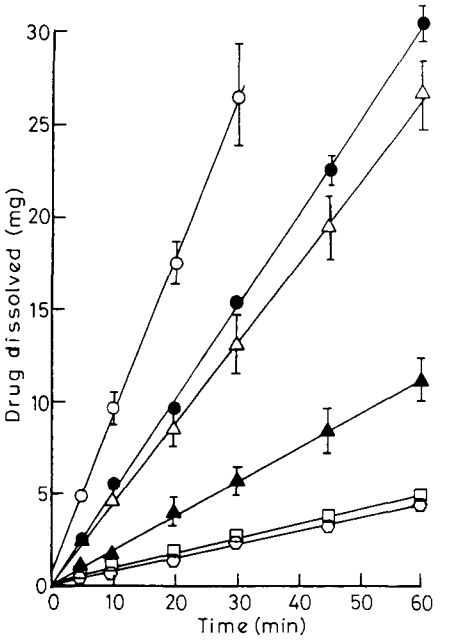

FIG. 2. Common-ion effect on the dissolution profiles of the sodium salt of REV 3164 in water from a surface area of 0·95 cm^2 at 25 °C. Sodium chloride solutions of 0 (water only) (○), 0·01 (●), 0·02 (△), 0·05 (▲) and 0·10 M (□) concentrations, and 0·10 M sodium carbonate-bicarbonate buffer (pH 10) (⬡) were used. Each datum point represents the average ± s.d. of three determinations.

Table 2. Intrinsic dissolution rates (J/A) and ratios of intrinsic dissolution rates to solubilities (J/(AC_s)) of the sodium salt of REV 3164 in water at various sodium chloride concentrations and a temperature of 25 °C.

NaCl concentration in water (M)	J/A (mg cm^{-2} min^{-1})	(J/AC_s)[a] (cm min^{-1})
0	0·901	0·116
0·01	0·570	0·094
0·02	0·458	0·107
0·05	0·197	0·090
0·10	0·081	0·076
Sodium carbonate-bicarbonate buffer (0·1 M, pH 10)	0·072	0·110

[a] Values of C_s from Table 1 used.

phobic moeities which lie towards the surface of the 'stacks'. The presence of π-electron systems and slightly polar groups (e.g. ring nitrogen) facilitate this hydration. It is also known that inorganic ions undergo hydration (Amis 1975). Thus, the added electrolytes would destabilize the aggregates (reduce aggregation numbers) of drug molecules by competing for the water of hydration. This is analogous to the effect of salt solutions on non-electrolytes ('salting out' effect) (Long & McDevit 1952). Since the roles of the ionized moieties in the aggregation process is minor, the effect of counter-ions would also be minimal. In contrast, flexible chain surfactants and amphiphilic drugs form micellar aggregates. The added electrolytes increase the aggregation number of the ionized forms of such compounds by acting as counter-ions and thus reducing the repulsive interactions of charged heads (Attwood & Florence 1983; Attwood & Natarajan 1983; Attwood & Agarwal 1984; Atherton & Barry 1985).

Intrinsic dissolution rate

The dissolution profiles of the sodium salt of REV 3164 in water at various NaCl concentrations and in 0·1 M sodium carbonate-bicarbonate buffer (pH 10) are given in Fig. 2. The slopes of the profiles decreased with the increase in NaCl concentration or by the presence of the buffer. The relationship between the dissolution rate (J) and the solubility (C_s) of a drug may be expressed by the Noyes-Whitney equation:

$$J = DA(C_s - C)/h \quad (4)$$

where D, A, h and C are, respectively, the diffusion coefficient, the surface area of the dissolving pellet, the diffusion layer thickness, and the concentration of the drug. Under sink condition ($C_s \gg C$), equation 2 reduces to

$$J/(AC_s) = D/h \quad (5)$$

If A is kept constant and D and h are assumed to be constant $J/(AC_s)$ should be constant. Table 2 shows that $J/(AC_s)$ values at different NaCl concentrations and in the buffer remain approximately constant. These results, therefore, show that any decrease in solubility of the sodium salt of a drug due to the common ion effect would also decrease its dissolution rate. This effect should be considered carefully when selecting dissolution media for solid dosage forms and in comparing dissolution data generated by using different media.

REFERENCES

Anderson, B. D., Conradi, R. A. (1985) J. Pharm. Sci. 74: 815–820

Amis, E. S. (1975) in: Dack, M. R. J. (ed.) Solutions and Solubilities, Part I. John Wiley & Sons, New York, pp 105–193

Atherton, A. D., Barry, B. W. (1985) J. Colloid Interfac. Sci. 106: 479–489

Attwood, D., Agarwal, S. P. (1984) J. Pharm. Pharmacol. 36: 563–564

Attwood, D., Florence, A. T. (1983) Surfactant Systems. Chapman & Hall, London, pp 124–161

Attwood, D., Natarajan, R. (1983) J. Pharm. Pharmacol. 35: 317–319

Bogardus, J. B., Blackwood, R. K. (1979) J. Pharm. Sci. 68: 188–194

Chowhan, Z. T. (1978) Ibid. 67: 1257–1260

Connors, K. A. (1975) A Textbook of Pharmaceutical Analysis, 2nd ed., Wiley-Interscience, New York, USA, pp 184–186

Haugen, G. R., Hardwick, E. R. (1963) J. Phys. Chem. 67: 725–731

Khandwala, A., Dally-Meade, V., Jariwala, N., Huang, F. (1984) Int. Arch. Allergy Appl. Immunol. 73: 65–70

Liebowitz, M., Gordon, R. J., Sonnino-Goldman, P., Wolf, P. S. (1984) Arch. Int. Pharmacodyn. Ther. 271: 135–154

Long, F. A., McDevit, W. F. (1952) Chem. Rev. 51: 119–169

Martin, A., Swarbrick, J., Cammarata, A. (1983) Physical Pharmacy, 3rd ed., Lea & Febiger, Philadelphia, PA, USA, pp 181–182

Mukerjee, P. (1973) J. Pharm. Sci. 63: 972–981

Niebergall, P. J. (1980) in: Osol, A., (ed.) Remington's, Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, USA, p. 223

Scientific Tables (1970) 7th ed., Ciba-Geigy Ltd, Basle, Switzerland, p. 281

Serajuddin, A. T. M., Jarowski, C. I. (1985) J. Pharm. Sci. 74: 148–154

Serajuddin, A. T. M., Mufson, D. (1985) Pharm. Res. 2: 65–68

Serajuddin, A. T. M., Rosoff, M. (1984) J. Pharm. Sci. 73: 1203–1208

Strykowski, J. S., Pandit, N. K. (1986) Am. Pharm. Assoc. 133rd Annual Meeting, San Francisco, CA, USA, Abstract No. P-8

Thoma, K., Albert, K. (1983) Die Pharmazie 38: 697–708

Wood, J. H., Syanto, J. E., Lettermann, H. (1965) J. Pharm. Sci. 54: 1068