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Solubilities and intrinsic dissolution rates of sulphamethoxazole and trimethoprim

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The influence of pH on the dissolution rates and solubilities of sulphamethoxazole and trimethoprim have been examined. Sulphamethoxazole was evaluated in buffers of ionic strength 0·5 mol dm^{-3} over the pH range 0·45–7·8 and at 25, 32 and 37 °C. The minimum solubility of sulphamethoxazole was 28·1 mg/100 mL at pH 3·22 and 25 °C. Solubilities increased significantly with both increased and decreased pH. Intrinsic dissolution rates demonstrated a linear relationship with the solubility data. Trimethoprim solubility was both buffer- and pH-dependent. In both water and hydrochloric acid solution at 32 °C the solubility of trimethoprim increased from 50 mg/100 mL in water at pH 8·54 to a maximum of 1550 mg/100 mL at pH 5·5. This maximum solubility was in excess of that predicted theoretically and may be due to supersaturation. Below pH 2 the solubility of protonated trimethoprim diminished from 1125 mg/100 mL with decreasing pH. This was due to the common ion effect. Intrinsic dissolution rates increased as pH was decreased with hydrochloric acid from 6·00 to 1·78, but decreased at pH 1·48 due to the common ion effect. Dissolution profiles of trimethoprim showed complex patterns dependent upon pH. The profile was zero-order at pH 6·00 and became distinctly stepwise at pH 5·5, this effect becoming less pronounced at lower pH values. This was reconciled in terms of the rate of formation of trimethoprim hydrochloride on the surface of the disc and the differing dissolution rates of this species and trimethoprim. A simple relationship between solubility and dissolution rate was not observed.

There has been interest in the solubilities and dissolution profiles of weak bases and their hydrochloride salts in the presence of buffers and in hydrochloric acid solutions (Miyazaki et al 1979, 1980: Serajuddin & Rosoff 1984; Serajuddin & Jarowski 1985). Those studies have reported unusual pH solubility characteristics, frequently associated with large changes in measured solubilities over a narrow pH range. Also, solubilities much lower than those theoretically predicted were reported at low pH values.

Dissolution studies on bases and their hydrochloride salts in hydrochloric acid solutions have shown that both solubilities and dissolution rates were greater for the free bases than for their hydrochloride salts (Miyazaki et al 1981). Also the dissolution rates for the free bases increased as pH values decreased, whereas for the salts the reverse was noted (Miyazaki et al 1975). These results may indicate that any basic drug of low solubility which can form a hydrochloride salt may give rise to variable dissolution rates in-vivo when given orally. Trimethoprim (TMP) is such a drug and therefore a study of its solubility and dissolution behaviour over a range of pH values would contribute to the understanding of the behaviour of this drug in man.

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Sulphamethoxazole (SMX) shows amphoteric properties and consequently will have two dissociation constants. Therefore a plot of either solubility or dissolution rate against pH would be expected to show a minimum. Differences in absorption rates of SMX which have been reported (Patel & Welling 1980) may be due to pH-dependence of both dissolution rate and solubility. Knowledge of these parameters would also be useful.

MATERIALS AND METHODS

Trimethoprim (Batch lot 101F-0243, Sigma Chemicals, USA) and sulphamethoxazole (Batch lot 22F-0415, Sigma Chemicals) were used as received. All other chemicals were AR grade. Water was deionized, passed through a Milli-Q apparatus (Millipore, USA) and had a specific conductivity of less than $5{\cdot}5 \times 10^{-6}$ ohm^{-1} cm^{-1}.

Solubility studies

Solubilities were determined by equilibrating excess of the drugs (SMX and TMP) in buffer solutions at the relevant temperatures (±0·1 °C) and in solutions of HCl (TMP only) at one temperature (32 °C). Ionic strengths of buffers were calculated and adjusted to 0·5 by the addition of sodium chloride. Samples were filtered and pH values of filtered solutions were measured, and absorbances were read in a UV

spectrophotometer after dilution (Varian Techtron 635, Australia). For TMP, absorbances were read at 276 nm which is the isosbestic point for TMP/$TMPH^+$. Absorbances of SMX were measured at 257 nm (SMX^-) or 265 nm (SMX, $SMXH^+$). Concentrations of dissolved species were calculated from calibration curves of TMP and SMX adjusted to the relevant pH (Activon Model 101, Australia).

Intrinsic dissolution rates

Intrinsic dissolution rates for TMP were measured in HCl solutions at 32 °C, over a range of pH values. For SMX, dissolution was carried out at 25 °C using appropriate buffers, and ionic strengths were calculated and adjusted to 0·5. Discs were prepared and analysed using an apparatus which has been described previously (Wall et al 1985). Discs had a diameter of 21·7 mm and were prepared using a force of 4×10^3 kg under vacuum. Dissolution rates were measured in triplicate. The discs were rotated at 100 rev min^{-1} in 900 mL of buffer or HCl solution. Samples of 10 mL were removed, with replacement, filtered, diluted, and the absorbances of the solutions were measured as above. For HCl solutions the pH values of the media were kept constant by the addition of 0·1 M HCl.

RESULTS AND DISCUSSION

SMX solubility

Solubilities of SMX, measured at 25, 32 and 37 °C are shown in Table 1. The solubilities increased with temperature. Also as pH decreases, solubilities go through a minimum value at pH 3·75 and then rapidly increase. Such behaviour has been reported for other amphoteric materials such as aminopenicillins (Tsuji et al 1978) and aminocephalosporins (Tsuji et al 1979). This is a reflection of the various species of SMX which exist at different pH values as follows:

$SMXH^+$	$\rightleftharpoons$	SMX	$\rightleftharpoons$	SMX^-
protonated species		molecular species		deprotonated species
low pH values		intermediate pH values		higher pH values

The un-ionized species (SMX) is much less soluble than either of the two ionized species, as would be expected.

Thermodynamic parameters for the solubility of each species were calculated by standard methods accounting for the pH change with temperature by the methods of Sunderland & Watts (1984). These data are: $\Delta H° = 5{\cdot}1$ kJ mol^{-1} and $\Delta S° = 0{\cdot}7$ J K^{-1} mol^{-1} for $SMXH^+$; $\Delta H° = 28{\cdot}4$ kJ mol^{-1} and $\Delta S° = 38{\cdot}8$ J K^{-1} mol^{-1} for SMX and $\Delta H° = 12{\cdot}2$ kJ mol^{-1} and $\Delta S° = 9{\cdot}6$ J K^{-1} mol^{-1} for SMX^- where $\Delta S°$ values were calculated at 305·15 K (32 °C). These data indicate little temperature dependency or structural change occurring for $SMXH^+$ species. The molecular species shows a greater temperature effect which is accompanied by a compensatory increase in entropy. Possibly the

Table 1. Solubilities of sulphamethoxazole in aqueous buffers at an ionic strength of 0·500 mol dm^{-3} and 25, 32 and 37 °C.

Buffer (concn)	pH[a] (at equilibrium)	Solubility (±1 s.d.) mg 100 mL^{-1} 25 °C	32 °C	37 °C
HCl	0·45	620·7 ± 9·3	692·7 ± 5·3	752·7 ± 4·1
HCl	1·15	120·8 ± 3·6	152·0 ± 3·1	182·9 ± 1·0
Tartrate (0·20 mol dm^{-3})	2·08	38·0 ± 0·7		
	2·24		42·1 ± 0·3	
	2·32			51·9 ± 0·2
Glycine (0·085 mol dm^{-3})	3·22	28·1 ± 0·2		
	3·36		38·0 ± 0·7	
	3·43			46·2 ± 0·5
Acetate (0·10 mol dm^{-3})	3·94	29·0 ± 0·3		
	4·04		37·7 ± 0·1	
	4·11			50·8 ± 0·1
Phosphate (0·15 mol dm^{-3})	5·41	39·1 ± 0·5		
	5·45		50·9 ± 0·3	
	5·48			61·3 ± 0·3
Phosphate (0·15 mol dm^{-3})	7·17	611·2 ± 0·9		
	7·16		707·5 ± 9·0	
	7·16			825·0 ± 3·2
Borate (0·15 mol dm^{-3})	7·83	3480·2 ± 61·5		
	7·81		3674·6 ± 8·6	
	7·79			3766·2 ± 48·5

[a] A negligible variation of a_{H+} occurs within this temperature range in HCl buffers.

more hydrophobic nature of this species in solution contributes to these effects. The deprotonated species solubility reaction again gives small thermodynamic parameters.

Amphoteric substances such as SMX have two dissociation constants, and the total solubility S_T can be calculated:

$$S_T(pH < pH_{S_0}) = S_0([H^+]/K_{a1} + 1) \quad (1)$$

$$S_T(pH > pH_{S_0}) = S_0(K_{a2}/[H^+] + 1) \quad (2)$$

where S_0 is solubility of the molecular form (28 mg/100 mL).

Using these equations, data for pK_{a1} and pK_{a2} were determined at the pH values where solubilities were experimentally determined. The pK_{a1} and pK_{a2} values determined at 25 °C by this method were 1·69 ± 0·07 and 5·81 ± 0·05, respectively. Equations (1) and (2) also enable a theoretical pH solubility profile to be generated using the above data.

Theoretical profiles at each temperature agree well with the experimentally determined data (Table 1). Setting $K_a = [H^+]$ reduces equations (1) and (2) to $S_T = 2S_0$ and hence pK_{a1} and pK_{a2} can be obtained at these pH values. Data so obtained were in acceptable agreement with those quoted above, which confirm the values of 1·76 and 5·81 previously reported (Koizumi et al 1964). The nature of the data in Table 1 indicates that changing the buffer does not affect the solubility values of SMX except through alterations of pH. No evidence is apparent indicating any insoluble salt formation.

In solutions of very high acidity SMX can undergo a second protonation (Manzo & de Bertorello 1973). It was reported that the pK_a for this reaction is −3·52. The solubility data obtained in hydrochloric acid solutions in the present study would not be influenced by such an equilibrium.

TMP solubility

Solubilities of TMP in the various buffer solutions are included in Fig. 1 at 32 °C. Solubility was also studied at 25 and 37 °C in the same solutions and the results indicated that all solubilities increased with temperature. However, the solubilities appear to be buffer dependent as well as pH dependent, which may indicate the formation of salts, making comparison with theory difficult. No attempt was made to isolate these species and determine their composition, and thermodynamic parameters were therefore not calculated. The solubility of TMP was further studied at 32 °C in hydrochloric acid solution. The solubility values obtained are reported in Fig. 1, which indicates the solubility/pH relationship.

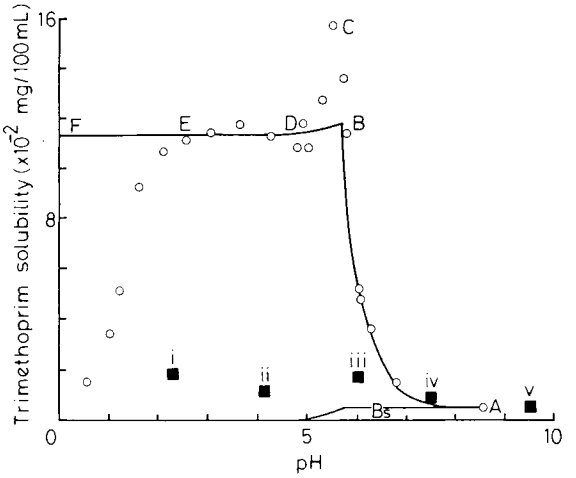

FIG. 1. Solubility of trimethoprim in hydrochloric acid solutions (○) at 32 °C. The lines are derived from equations 3 and 4 and data in the text. B_s is the solubility of the un-ionized species. Also illustrated (■) is the solubility of trimethoprim at 32 °C in (i) tartrate, (ii) acetate, (iii) phosphate, (iv) phosphate and (v) borate buffers.

Equations have been developed which express the solubility, S_T, of salt and base at any pH value (Kramer & Flynn 1972).

$$S_T(pH < pH_{max}) = [BH^+]_s + [B] = [BH^+]_s (1 + K_a/[H^+]) \quad (3)$$

and

$$S_T(pH > pH_{max}) = [BH^+] + [B]_s = [B]_s (1 + [H^+]/K_a) \quad (4)$$

where $[BH^+]$ and $[B]$ are concentrations of ionized and un-ionized species, respectively. The subscript refers to a saturated species. Since the total solubility at any pH value is the sum of the solubility of one species and the concentration of the other required to satisfy equations (3) and (4), these equations represent the cases where salt and free base, respectively, are solubility limiting. Insertion of appropriate data into equations (3) and (4) results in two separate curves which will intersect at a point which is the pH of maximum solubility for the drug, i.e. the sum of $[B]_s$ and $[BH^+]_s$ (Fig. 1). The solubility of TMP in water at 32 °C was found to be 50 mg/100 mL and the pH of this saturated solution in water was found to be 8·54. At this pH value TMP is predominantly in the un-ionized form. The pK_a was calculated at each experimental pH studied and the value found was 7·02 ± 0·05 which agrees well with the literature value of 7·12 determined at 20 °C (Roth & Strelitz 1969). Application of equation (3) employing the above data generates the solid line AB (Fig. 1) which is in good agreement with the

experimental data. In the pH region 5·0 to 2·5 (DE) the experimental data show a plateau region with a mean solubility of 1125 mg/100 mL. This value is the saturation solubility of TMP.HCl. Application of equation (4) with the above value gives the theoretical line FEDB which exhibits a maximum solubility, the sum of $[B]_s$ and $[BH^+]_s$, of 1175 mg/100 mL at a pH of 5·65.

The maximum measured solubility was 1550 mg/100 mL (C, Fig. 1). In the region of pH 5·5 a number of solubility determinations gave values in excess of experimental error associated with the estimated values (ABD, Fig. 1). Repeated determinations of the solubility of TMP in the pH region 5·0 to 5·5 gave the same values within experimental error. This persisted even after up ω 45 h of equilibration. Excess solid was removed from a solubility determination at pH 5·40. Potentiometric titrations, using Ag/AgCl and calomel electrodes with silver nitrate as titrant, showed a 1:1 molar ratio of TMP and HCl. This would appear to exclude the possibility of a partially protonated species being formed near the pH maximum. Somewhat similar experimental data have been found recently for papaverine hydrochloride (Serajuddin & Rosoff 1984) and phenazopyridine hydrochloride (Serajuddin & Jarowski 1985). Those workers have described that occurrence was due to supersaturation of one or more of the species present. Another possibility is the formation of a more soluble association complex near the pH of maximum solubility. This phenomenon requires further investigation. At the pH of maximum solubility, addition of small amounts of hydrochloric acid results in the formation of TMP.HCl above its solubility, and precipitation will occur to restabilize the equilibrium (Bogardus & Blackwood 1979). Excess solid base will also dissolve to re-establish the equilibrium. Further small decreases in pH caused by addition of acid will be nullified as the system returns to the pH of maximum solubility. The sequence of events described is as follows:

$$TMP_{(solid)} \rightleftharpoons TMP_{(soln)} + TMP.H^+ + Cl^- \rightleftharpoons TMP.HCl_{(solid)} \quad (5)$$

Eventually continued addition of HCl will result in all solid TMP being exhausted and then equation (3) will determine solubility.

Below pH 2 solubility decreased markedly (Fig. 1). Potentiometric examination of excess solid removed from a solubility determination at pH 1·2 again only showed the presence of a 1:1 molar ratio of TMP:HCl. The decreased solubility is due primarily therefore to the common ion effect. As HCl concentration increases, then the solubility of TMP.HCl is depressed. Common ion effects may be quantified either by the Setschenow salting out equation or by use of solubility product calculations. Bogardus (1982) has suggested that k, the salting out constant, varies with solubility and rate of change of solubility and that this treatment cannot be used generally for the analysis of common ion effects. Consequently, the solubility product approach has been adopted as follows:

For TMP.HCl the solubility equilibrium is

$$[TMP.HCl]_{solid} \rightleftharpoons [TMPH^+]_s + [Cl^-] \quad (6)$$

$$K^\circ_{sp} = [TMPH^+]_s[Cl^-] \quad (7)$$

where K°_{sp} = solubility product. Since $S_T = [TMPH^+]_s + [TMP]$ and since $[TMPH^+] \gg [TMP]$ then

$$K'_{sp} = S_T[Cl^-] \quad (8)$$

where K'_{sp} is the apparent solubility product (Serajuddin & Jarowski 1985).

In this derivation concentrations are used since activities are unavailable for these systems. The $[Cl^-]$ is the total chloride ion concentration present in the system and since only monovalent cations are present, this is equal to the ionic strength.

The mean value for K'_{sp} over the pH range 0·54 to 2·10 was $1{\cdot}5 \times 10^{-3} \pm 1{\cdot}6 \times 10^{-4}$ $(mol\ dm^{-3})^2$. K°_{sp} is related to K'_{sp} by equation (9).

$$K^\circ_{sp} = \frac{K'_{sp}}{(1 + K_a/[H^+])} \quad (9)$$

Since in the pH region studied $K_a \ll [H^+]$, $(\leqslant 1 \times 10^{-5})$, then $K^\circ_{sp} \simeq K'_{sp}$ and this value is approximately the true solubility product. The agreement between solubility product values as pH changes is reasonable $(\pm 1{\cdot}6 \times 10^{-4})$ and suggests that decrease in solubility is due to the common ion effect. Theoretically, the amount by which the solubility decreases cannot be greater than the amount of common ion added. If this is so, then the observed effect is not due to a common ion concentration change and some other phenomenon such as, for example, self association, may be responsible (Bogardus & Blackwood 1979).

Dissolution studies

Dissolution of SMX. Dissolution studies on SMX were carried out in triplicate at four pH values, i.e. 1·23, 4·06, 5·41 and 7·60 at 100 rev min^{-1}. The pH values were attained using appropriate buffers adjusted to an ionic strength of 0·50. Least square analysis of the dissolution rate data shown in Fig. 2 indicates

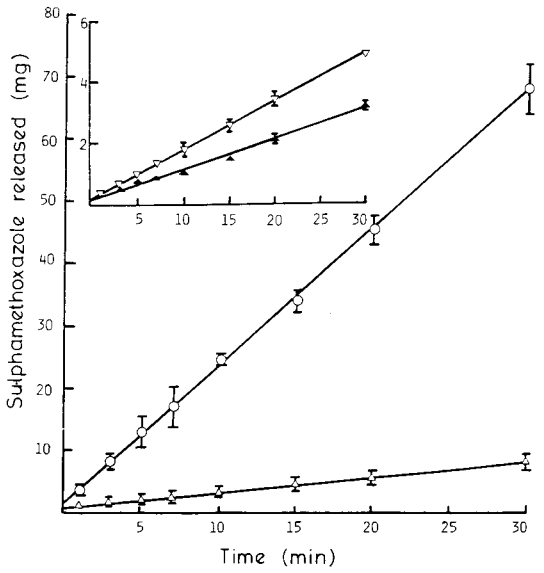

FIG. 2. Intrinsic dissolution rates (mean ±2 s.d.) of sulphamethoxazole in aqueous buffer solutions at 100 rev min^{-1} and 25 °C, and pH 1·23 △——△; 4·06 ▲——▲; 5·41 ▽——▽; and 7·60 ○——○.

correlation coefficients ≥ 0·998 for the linear relationships.

The rotation speed corresponds to a Reynolds Number (Re) of approximately 700 as defined by: $Re = r^2 \omega/v$ where r is the radius of the disc, ω is the angular velocity in radians per unit time, and v is the kinematic viscosity of the medium. This is well below that quoted by Levich (1962) for transition from laminar to turbulent flow at the disc surface.

As pH is increased from 1·23, dissolution rate is decreased, initially, and then rises at the highest pH. A plot of intrinsic dissolution rate against solubility shows a linear relationship with a correlation coefficient greater than 0·99. A U-shaped relationship between the intrinsic dissolution rates and pH exists. A similar relationship has been found for sulphamethizol (Nicklasson et al 1981). These data indicate that SMX obeys the Noyes-Whitney relationship where dissolution rate is directly proportional to saturation solubility.

Linear regression analyses of the dissolution curves show that in all cases the lines do not pass through zero. The higher the dissolution rate the higher is the intercept value, which suggests that natural convection during the time lag in commencing rotation of the discs may be at least partly responsible for this effect.

Since the pK_a values for SMX are 1·69 and 5·81, it would be expected that data obtained at pH 4·06 would reflect the dissolution rate of the molecular species and the bulk pH would reflect that of the solid–liquid interface since little surface ionization occurs at this pH. At low pH SMX will initially accept protons in the formation of the acid salt ($SMXH^+$) and at higher pH values release protons in the formation of SMX^-. These surface reactions could give rise to lower and higher surface pH values, respectively, relative to the bulk pH (Mooney et al 1981). However, those workers indicate that pH at the surface of the disc can be controlled by a swamping effect of the buffer. Since the buffer concentrations in this study were high, this is a tenable explanation for the linear relationship found between intrinsic dissolution rate and solubility.

Dissolution of TMP. Dissolution data for TMP in hydrochloric acid solutions at 32 °C were obtained at the pH values of 1·48, 1·78, 2·93, 5·50 and 6·00. Maintenance of the bulk pH was effected by addition of HCl automatically or manually. Constant ionic strength was not maintained. Dissolution profiles for TMP are shown in Fig. 3. At pH 6·00 and pH 2·93 dissolution was zero order with rates equivalent to $7{\cdot}30 \times 10^{-2}$ and $1{\cdot}34 \times 10^{-1}$ mg cm^{-2} min^{-1}, respectively. At other pH values the dissolution rates were no longer zero order and the shape of the curves distinctly non-linear. Visible layers were deposited on part of these discs. Careful removal of these layers from the discs' surfaces, followed by potentiometric titrations as before, indicated that the layers were TMP.HCl. The dissolution rates, however, all increased with decreasing pH except at pH 1·48. This reduction in dissolution rate was presumably due to the common ion effect, diminishing the solubility (Fig. 1) and hence the dissolution rate. This trend is similar to that found in other studies involving the influence of hydrochloric acid concentrations on the dissolution rates of free bases (e.g. Serajuddin & Jarowski 1985).

The stepwise nature of some of the dissolution rate plots could be explained in terms of the different solubilities of TMP and the TMP.HCl layer formed. Each substance could predominate at different times during a dissolution run. Other workers (Levy & Procknal 1962; Serajuddin & Jarowski 1985; Wall et al 1985) have similarly reported the formation of such layers involving other substances, and markedly affecting the dissolution rates. Anderson & Pitman (1980) also found dissolution rates that were not in conformity with the Noyes-Whitney equation. This finding was ascribed to the slowness of precipitation of the chloride salt produced when a tartrate salt was

dissolved in 0·1 mol dm^{-3} HCl. Mooney et al (1981) have also considered the species present in the diffusion layer during dissolution reactions. Their model would indicate that with TMP dissolution, diffusion of protons would be dominant at low pH (i.e. pH 1·48 and 1·78), whereas at higher pH values the total flux would become dependent upon all species present (TMP, H^+ and OH^-). These effects may contribute to the complicated dissolution profiles found (Fig. 3). However, deposition of TMP.HCl onto the disc surface is probably the major effect causing these step-wise and non-linear dissolution profiles.

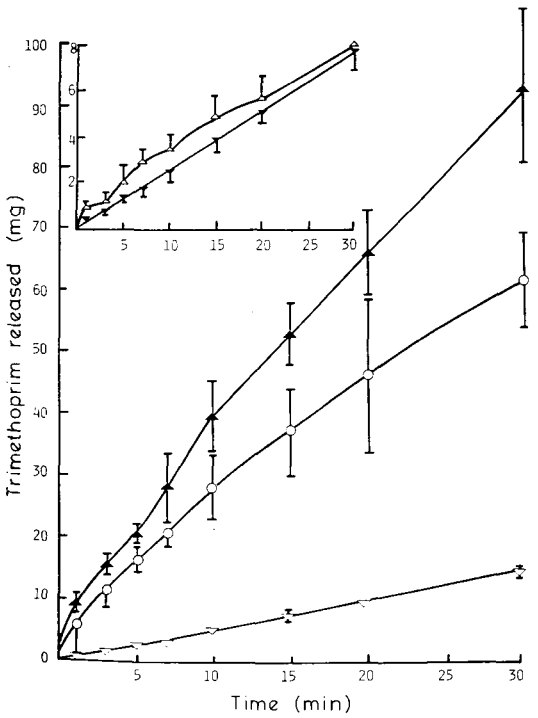

FIG. 3. Intrinsic dissolution rates (mean ± 2 s.d.) of trimethoprim in hydrochloric acid solutions at 100 rev min^{-1} and 32 °C, and pH 1·48 ○——○; 1·78 ▲——▲; 2·93 ▽——▽; 5·50 △——△; and 6·00 ▼——▼.

This study indicates marked variation in solubilities of sulphamethoxazole and trimethoprim with pH. On both a molar basis and mg/100 mL, the solubility of TMP is approximately twice that of SMX at pH 1·0. At pH 5·0, TMP is approximately twenty-fold more soluble than SMX. Hence although these drugs are formulated with five-fold more sulphamethoxazole than TMP, solubilities and the conversion of TMP to $TMPH^+$ and different volumes of distribution (Kaplan et al 1973) complicate the behaviour of these drugs in man. This study provides evidence that the dissolution rates of these drugs may be pH-dependent in man and this may contribute to the variable absorption rates found by Patel & Welling (1980).

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