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COMMUNICATION

DISSOLUTION RATES OF TRIMETHOPRIM-SULPHAMETHOXAZOLE AND TRIMETHOPRIM TABLETS IN AQUEOUS MEDIA

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ABSTRACT

Dissolution rates of trimethoprim and sulphamethoxazole from combination tablets showed a rapid release of trimethoprim in acid media from all formulations. Sulphamethoxazole showed a more variable release pattern and faster release in dilute acid medium compared with the less acidic simulated gastric fluid. Tablets containing only trimethoprim showed a release rate into hydrochloric acid media that was dependent upon pH. Approximately twice the amount of trimethoprim was released in twenty minutes at pH 1.32 compared with pH 6.50.

INTRODUCTION

Ahmad and Ishrat[1] found a high degree of variation in the dissolution times of five commercial trimethoprim-sulphamethoxazole (TMP-SMX) tablets. It has also been reported that the grade of carboxymethylcellulose used as disintegrant significantly altered the dissolution rates of SMX tablets[2].

The present study involves an evaluation of the dissolution rates of SMX and TMP from combination formulations of these drugs and a study of the influence of pH on the dissolution rate of TMP from TMP tablets.

METHODS

Tablet formulations used were: Trimethoprim 160 mg and Sulphamethoxazole 800 mg: Septrin Forte® Wellcome Australia Batch 74751; Bactrin DS® Roche Products Australia Batch D4974; Trib ds® Protea, Australia Batch 821019X12. Trimethoprim 300 mg, Triprim® Wellcome Australia Batch 79911.

All other materials were of AR grade and water was deionised water passed through a Milli-Q (Millipore) apparatus and had a specific conductivity of $< 5.5 \times 10^{-6}$ Ohm^{-1} cm^{-1}. Simulated Gastric Fluid (SGF) and dilute hydrochloric acid media (DHAM) were of USP[3] standard.

Dissolution rates were evaluated using an apparatus that complied with USP requirements[3] (Hanson, Ca.). TMP and SMX in combination were measured by an HPLC method and SMX alone by ultra-violet spectrophotometry. Detailed methods have been reported elsewhere[4,5].

RESULTS AND DISCUSSION

Trimethoprim-Sulphamethoxazole Tablets

No dissolution test is given in current compendia[3] for SMX in combination with TMP. Hence both SGF and DHAM were employed in these evaluations. In all studies a rapid release of TMP occurred from the combined formulations, greater than 93% being released in 20 minutes. Dissolution rates of SMX from these formulations (Table 1) were slower than TMP and more variable. Release rates for SMX were faster in DHAM compared with SGF. This phenomenon was in accordance with the solubility profile for SMX[4]. Some variation in the rate of release was evident between the brands with Trib ds® showing the slowest dissolution rates.

The time for 50 per cent release in either medium showed little variation when fitted to a logarithmic-normal distribution function[6] (Figure 1). However, differences in the slope values (σg) were evident, particularly in the latter stages of dissolution. These differences were apparent when the times for 63.2 per cent release were obtained (Table 1).

Similar data for the time for 63.2 per cent release were obtained from the Langenbucher equation[7]. All formulations tested complied with the USP requirements[3] that no less than 50 per cent labelled amount of SMX dissolves in DHAM within 20 minutes. In the less acidic medium SGF, this limit was barely achieved with two of the formulations, which agrees with the intrinsic dissolution data for SMX where the dissolution rates are directly proportional to solubility[4].

TABLE 1

Dissolution of Sulphamethoxazole at 100 rpm at 37°C into Specified Media from Trimethoprim-Sulphamethoxazole Tablets

Brand	Percentage Released in 20 min.		$t_{50\%}$ (min.)			$t_{63.2\%}$ (min.)	
	DHAM(a)	SGF(b)	DHAM(c)	(σg)	SGF (σg)	DHAM	SGF
Bactrim DS	82	59	7	(3)	12 (9)	9	27
Septrin Forte	70	50	7	(7)	12 (20)	14	44
Trib ds	67	49	7	(12)	21 (24)	15	68

(a) Dilute hydrochloric acid medium

(b) Simulated gastric fluid

(c) Data obtained by extrapolation

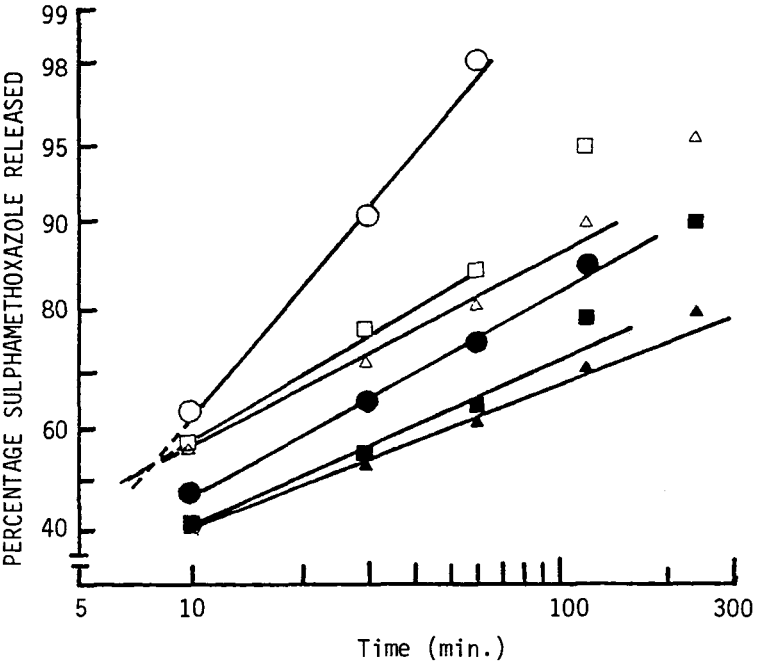

FIGURE 1

Logarithmic-normal dissolution rates of sulphamethoxazole from trimethoprim-sulphamethoxazole tablets in dilute hydrochloric acid medium (open) and simulated gastric fluid (closed) Bactrim DS (○●) Septrin Forte (□■) Trib ds (△▲).

Trimethoprim Tablets

Dissolution rates of trimethoprim tablets increased with decreased pH (increased concentration) of the hydrochloric acid dissolution media as shown in Table 2. The data are illustrated in Figure 2 using the logarithmic-normal function[5]. Similar data, within experimental error, could be obtained using the Langenbucher equation[6].

The dissolution profiles indicate little difference in dissolution rates when the pH decreases from 6.50 to 5.50. This correlates well with intrinsic dissolution data in the pH range 6.0 to 5.5, although the profile at pH 5.5 was complex[4]. Concentrations of H^+ ions in the diffusion layer may not have changed sufficiently to affect dissolution rates. A large increase in the solubility of TMP occurred within this pH range[4].

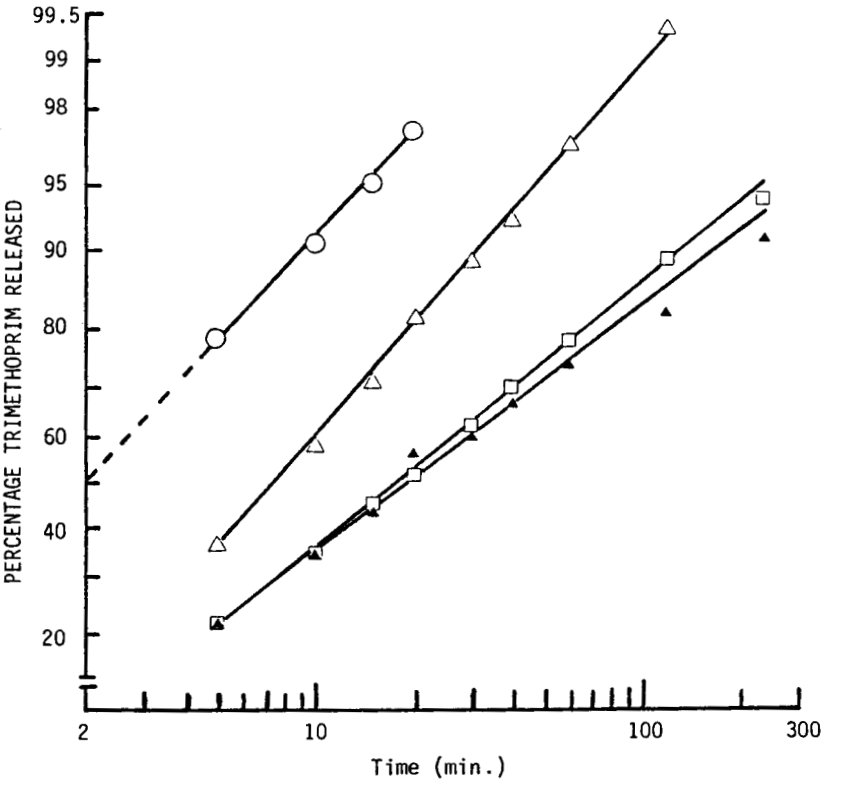

FIGURE 2

Logarithmic-normal dissolution rates of trimethoprim from trimethoprim tablets in hydrochloric acid medium pH 1.32 (○), pH 3.00 (△), pH 5.5 (□), pH 6.5 (▲).

TABLE 2

Dissolution Rates of Trimethoprim from Trimethoprim Tablets into Hydrochloric Acid Media at 32°C and 100 rpm. Also Indicated is the Time to Achieve 50% of Dissolution and the Geometric Standard Deviation (σg)

pH	Percentage released in 20 min.	$t_{50\%}$ (min.)	(σg)
1.32	99.4	2[a]	(3.3)
3.00	83.5	8	(2.7)
5.50	57.8	19	(5.3)
6.50	52.2	18	(4.6)

(a) Extrapolated from data obtained at longer time intervals

At lower pH values the dissolution rates of the tablets increased markedly, being of the same order as those found for intrinsic dissolution, but not correlating well with solubility data for trimethoprim[4]. This lack of correlation may be due to interference by trimethoprim hydrochloride at the dissolution interface[4] or to complex changes in the diffusion layer[8]. The dissolution profiles obtained for TMP tablets are smooth, giving no indication of the stepwise relationship found with the intrinsic dissolution profiles at pH 5.5, 1.78 and 1.48[4]. Formulation factors in the tablets may explain the differences. Both sets of data showed a lack of correlation with solubility in this lower pH region. The rate of dissolution was also markedly affected by the concentration of hydrochloric acid in the dissolution media. These data may indicate a variable dissolution rate of TMP in the gastrointestinal tract dependent upon pH.

CONCLUSION

The dissolution rates of trimethoprim from both combined and simple tablets were rapid at low pH. The rates of dissolution were much lower at pH 5.50 and 6.50. Some variability in the release rate of sulphamethoxazole occurred between the formulations studied. The rate of dissolution was faster in the more acidic DHAM compared with SGF. These data have indicated that individual variation in gastrointestinal pH could give rise to different dissolution rates of these drugs in humans.

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