GI Absorption of Two Crystal Forms of Sulfameter in Man

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Abstract □ The GI absorption of two crystal forms of sulfameter in man was studied. The more energetic crystal form has an absorption rate about 1.4 times as great as that of the water-stable form. Results are discussed in relation to the free energy differences of the two crystal forms (calculated from dissolution rate studies), the viscosity of the medium, and the rate of agitation. The relationship of the results of the present *in vivo* absorption study to those of *in vitro* dissolution rate studies is also discussed.

Keyphrases □ Sulfameter polymorphs—GI absorption, man, related to dissolution rates □ Polymorphism, sulfameter—GI absorption, man, related to dissolution rates □ Absorption, GI—sulfameter polymorphs, man □ Bioavailability—sulfameter polymorphs, GI absorption, man

The dissolution behavior of different polymorphic forms of drugs and its relationship to drug availability and absorption were discussed in a number of publications (1–3). Results of these studies were generally in agreement that the lower the thermodynamic activity of a polymorph, the lower is its apparent solubility and, consequently, its absorption and vice versa.

The polymorphism of sulfameter[1] was recently described by Moustafa *et al.* (4). Form II, the more thermodynamically active crystal form, was found to have an apparent equilibrium solubility about 1.8 times that of the water-stable Form III in 0.1 *N* HCl at 30°. Experiments at 37° showed a decrease in this ratio to about 1.6, since higher temperatures were found to accelerate the transformation from Form II to Form III in aqueous suspensions.

The present study was concerned with the GI absorption of Forms II and III of sulfameter. The purpose was to determine if the previously reported differences in their *in vitro* dissolution behavior are reflected in their *in vivo* absorption in humans. This knowledge allows a better understanding of the correlation between differences in physicochemical properties of polymorphs and their bioavailability.

EXPERIMENTAL

Materials—Sulfameter crystal Forms II and III were prepared as previously described (4). The two forms were screened to a particle size of 80–90 μm. and identified by IR spectrophotometry immediately before use.

Absorption Study—One gram of either crystal form was suspended in a mixture of 25 ml. each of 20% mucilage of acacia and simple syrup. This mixture was immediately administered, after an overnight fast, to each of five normal healthy male volunteers (age: 28–33 with an average of 30 years; weight: 45–83 with an average of 70 kg.). This administration was followed by 50 ml. of water used to rinse the containing vessel. No food was permitted for 4 hr. after drug administration. Blood samples were taken at 0, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 60 hr. after administration, and the total sulfameter content in each sample was determined according to Bratton and Marshall (5). The same procedure was repeated for the other crystal form, with the same volunteers, 1 month later.

To test the effect of viscosity, Form III was administered in a third experiment to only two subjects. The same procedure was followed, except that 50 ml. of water replaced the suspending medium of mucilage of acacia and simple syrup.

Dissolution Rate Study—An *in vitro* dissolution rate experiment for Form III at 37° and 50 r.p.m. was carried out, as previously described (4), in 0.1 *N* HCl containing 5 ml. each of 20% mucilage of acacia and simple syrup/100 ml. of the dissolution medium. This was thought to provide conditions simulating those of the *in vivo* experiment, assuming stomach contents to be about 500 ml.

To test the effect of agitation, the *in vitro* dissolution rates of Forms II and III were determined as before (4) at 30° and 24, 48, and 72 r.p.m.

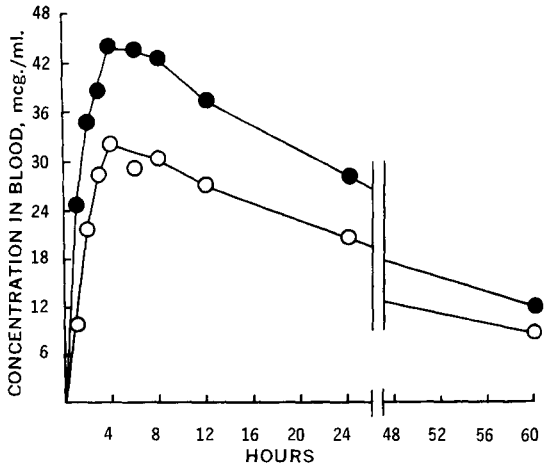

Figure 1—*Mean blood concentration curves of sulfameter crystal Forms II and III. Key:* ●, *Form II; and* ○, *Form III.*

RESULTS AND DISCUSSION

Blood concentration data of Forms II and III of sulfameter are shown in Table I. Figure 1 shows the mean blood concentration curves of the two forms. Blood samples taken just before drug

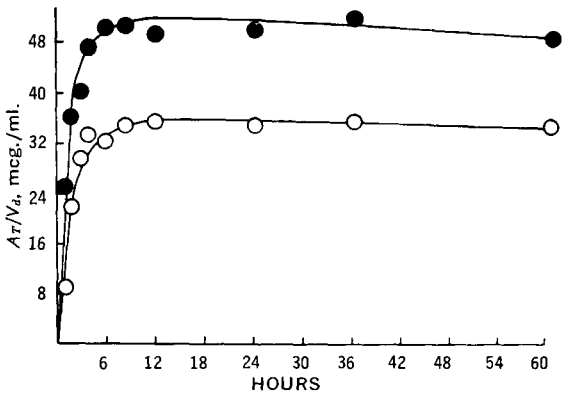

Figure 2—*Plots of* (A_T/V_d) versus *time for sulfameter crystal Forms II and III, where* A_T/V_d *represents the cumulative amount absorbed per apparent volume of distribution. Key:* ●, *Form II; and* ○, *Form III.*

[1] Previously used name: sulfamethoxydiazine.

Table I—Blood Concentration Data of Sulfameter Forms II and III

Subject	Crystal Form	Concentration of Sulfameter, mcg./ml. 1 hr.	2 hr.	3 hr.	4 hr.	6 hr.	8 hr.	12 hr.	24 hr.	36 hr.	60 hr.
H.S.	II	33	37.5	39.5	42.5	39.7	—[a]	32.5	27.1	22.5	12.8
	III	12.5	22	30.5	32	30	31.9	29	20.7	17	9.7
F.S.	II	25	32	37	42.6	42.1	41.4	37.4	27.3	21.5	10.9
	III	9.5	21.5	29.3	34	29.5	33.1	30	21.8	17	8.2
M.Y.	II	14	28.5	36.2	44	43.5	42.7	38.8	28.2	22.4	11.2
	III	9	22	27	31.5	29	30.6	27.6	20.2	16.2	8.4
I.A.	II	24.9	39	41	42.3	40.7	38.3	35	27.1	22	11.8
	III	8.5	18	26	30.5	29.5	29.6	27	19.5	15.9	8.5
A.R.[b]	II	27.5	37.5	39	49.5	48.8	48.1	44	31.7	25.2	13.8
	III	—	—	—	—	—	—	—	—	—	—
Mean	II[c]	24.9	34.9	38.5	44.2	43	42.6	37.5	28.3	22.7	12.1
	III[d]	9.9	20.9	28.2	32	29.5	31.3	28.4	20.6	16.6	8.7

[a] Blood sample not collected. [b] Subject A.R. did not take Form III. [c] Mean of five subjects. [d] Mean of four subjects.

Table II—Absorption Parameters of Sulfameter Forms II and III

Subject	Form	$(AUC^a)_{60\ hr.}$, mcg.-hr./ml.	$\left(\frac{A_T}{V_d}\right)_{max}^b$, mcg./ml.	K_A^c, hr.$^{-1}$	$\frac{(AUC)_{60\ hr.\ II}}{(AUC)_{60\ hr.\ III}}$	$\frac{(A_T/V_d)_{max\ II}}{(A_T/V_d)_{max\ III}}$	$\frac{K_{AII}}{K_{AIII}}$
H.S.	II	1573	47.7	0.689	1.31	1.32	1.39
	III	1205	36.3	0.495			
F.S.	II	1542	50.9	0.507	1.33	1.28	1.37
	III	1159	40.0	0.371			
M.Y.	II	1604	51.8	0.507	1.44	1.42	1.37
	III	1114	36.6	0.371			
I.A.	II	1507	47.9	0.689	1.36	1.37	1.53
	III	1111	35.0	0.449			
A.R.	II	1770	56.0	0.583	—	—	—
	III	—	—	—			
Mean	II	1599	50.9	0.595	1.36	1.35	1.42
	III	1147	37	0.422			

[a] Area under the curve. [b] Maximum or asymptotic value corresponding to A_∞/Va, where A_∞ is the amount of the drug eventually absorbed. [c] Availability rate constant.

administration proved to be free of sulfameter. The rates of availability of the two crystal forms (Figs. 2 and 3) were determined following the method of Wagner and Nelson (6–8). Table II summarizes and compares the absorption parameters for Forms II and III of sulfameter. The area under the blood concentration curve up to 60 hr. was included in Table II as an additional absorption parameter since it is a direct measure of the total amount of drug absorbed.

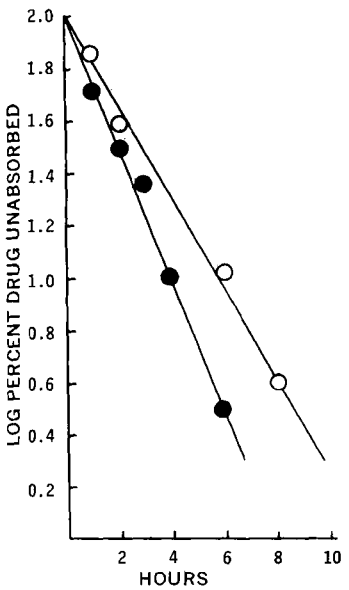

Figure 3—*Log percent sulfameter unabsorbed* versus *time. Key:* ●, *Form II; and* ○, *Form III.*

The absorption parameters for Form II (Table II) for individual subjects, as well as their means, were approximately 1.4 times as great as those of Form III. This ratio is somewhat lower than that (1.6) found *in vitro* for peaks of dissolution rate curves (apparent solubilities) of both forms at 37° (4).

Quantitative correlations between results of *in vitro* dissolution rate and *in vivo* absorption studies of some drug polymorphs vary from reasonable agreement to wide discrepancies. Tawashi (9), Poole *et al.* (10), and Haleblian *et al.* (11), for instance, reported agreement of the *in vitro* and *in vivo* findings for aspirin, ampicillin, and fluprednisolone crystal forms, respectively. Aguiar and Zelmer (3) reported lower *in vivo* differences, between polymorphs of mefenamic acid, than those found *in vitro*. On the other hand, Aguiar and Zelmer (3) and Ballard and Nelson (12) reported greater *in vivo* absorption rates for chloramphenicol palmitate and methylprednisolone polymorphs, respectively, than the corresponding *in vitro* dissolution characteristics. The discrepancy between *in vitro* and *in vivo* findings could be attributed to a number of factors. The most important of these factors are the differences in thermodynamic activities of the polymorphs (3), viscosity of dissolution media (13, 14) in relation to the actual viscosity at the site of absorption, particle size (15, 16) of the various crystal forms, degree of agitation (17) in relation to peristalsis in the GI tract, GI con-

Table III—Effect of Viscosity on the Dissolution and Absorption Parameters of Sulfameter Form III

Ratio	$(AUC^a)_{60\ hr.}$	$(A_T/V_d)_{max}^b$	K_A^c	Apparent Solubility
III with no additives / III with additives	1.38	1.41	1.37	1.47

[a] Area under the curve. [b] Maximum or asymptotic value corresponding to A_∞/Va, where A_∞ is the amount of the drug eventually absorbed. [c] Availability rate constant.

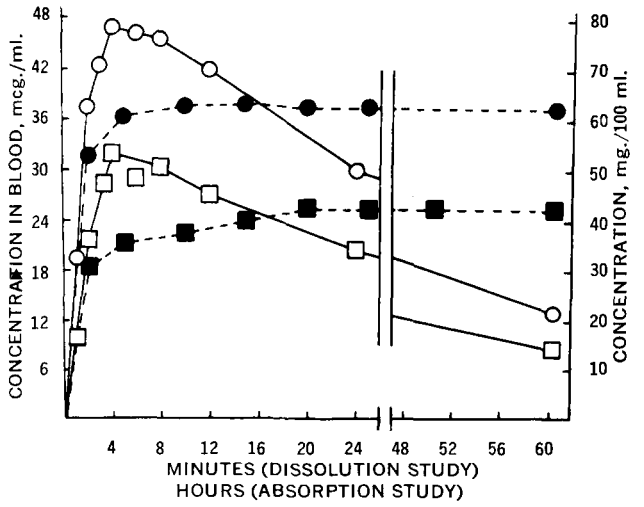

Figure 4—*Effect of viscosity on the absorption and dissolution of sulfameter Form III. Key:* ○, *blood concentration curve of Form III with no additives;* □, *blood concentration curve of Form III with additives;* ●, *dissolution curve of Form III with no additives; and* ■, *dissolution curve of Form III with additives.*

tents (18), fasting time before *in vivo* experiments, and other biological variables.

Aguiar and Zelmer (3) suggested that when the free energy differences, ΔG, between polymorphs were small (*e.g.*, two mefenamic acid crystal forms, $\Delta G_{30°} = -251$ cal./mole), there would be an insignificant difference in their absorption. On the other hand, when differences in ΔG were rather high (*e.g.*, two chloramphenicol palmitate polymorphs, $\Delta G_{30°} = -774$ cal./mole), a definite increase in the absorption of the more energetic polymorph (10-fold in the case of chloramphenicol palmitate polymorph B) was observed. The $\Delta G_{30°}$ for the two crystal forms of sulfameter of the present study is -291 cal./mole (4). It is expected, according to the findings of Aguiar and Zelmer (3), that perhaps only a slight difference in absorption rate would be observed. However, the present results show a significant difference in absorption of the two crystal forms.

The results (Fig. 1) show that the highest blood concentration of sulfameter reached was lower than that previously reported (19, 20). This might be due to differences in viscosity, particle size (the previous investigators probably used a micronized material while 80–90 μm. was used in the present study), and the presence of formulation additives that affect GI absorption. The effect of viscosity in retarding drug absorption in animals was discussed by Levy and Jusko (13) and Malone *et al.* (14). In the present study, removal of the viscosity-imparting materials (mucilage of acacia and simple syrup) was found to increase the apparent equilibrium solubility as well as the calculated absorption parameters of Form III by a factor of 1.4–1.5 (Table III and Fig. 4). However, it was necessary to use such additives in the absorption study since they suppressed the polymorphic transformation of Form II to Form III during the experiment.

Differences in dissolution rates of drug polymorphs were found to decrease at high agitation intensities (17, 21, 22). Although slight differences in dissolution rates of sulfameter Forms II and III were observed when the rate of agitation was varied from 24 to 72 r.p.m., no change in their apparent solubilities (peaks of dissolution rate curves) was noted. The large surface area available during the dissolution of sulfameter crystal forms (80–90 μm.), contrary to the limited surface available during dissolution from disks (17, 21, 22), may account for the relatively minor effects of agitation observed in the present study.

Marketed pharmaceutical preparations of sulfameter were found to contain mainly Form III (4). The results of the present study support the previous recommendation that, provided adequate measures are taken to prevent transformation of the metastable form, Form II is a better choice for use in dosage forms since it is the more biologically available crystal form.

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ACKNOWLEDGMENTS AND ADDRESSES

Received January 4, 1972, from the *Department of Pharmaceutics, Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt.*

Accepted for publication May 30, 1972.

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