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Succinylsulfathiazole Crystal Forms II: Effect of Additives on Kinetics of Interconversion

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Abstract ☐ The effect of various additives on the rate of transformation of the metastable anhydrous succinylsulfathiazole Form I to the water-stable dihydrate Form II in aqueous suspensions was studied. Some structurally related compounds, viscosity-imparting agents, surfactants, and coloring agents were used as possible transformation retardants. The effect of including seeds of Form II in the presence and absence of additives is also discussed. Some additives, *e.g.*, methylcellulose and phthalylsulfathiazole, showed significant transformation-retarding effects. Other additives, *e.g.*, sulfanilamide and glycerin, increased the rate of transformation. Coloring agents had only slight effects. Utilization of the results in the formulation of physically stable aqueous suspensions of succinylsulfathiazole is discussed.

Keyphrases ☐ Succinylsulfathiazole—crystal forms, interconversion, effect of structurally related compounds, viscosity-imparting agents, surfactants, and coloring agents ☐ Crystal forms—succinylsulfathiazole, effect of additives on interconversion

Succinylsulfathiazole crystal forms, their preparation, characterization, interconversion, and kinetics of transformation under standard conditions, were previously described (1). It was concluded (1) that the formulation of physically stable aqueous suspensions of succinylsulfathiazole may be achieved in one of two ways. The first involves the use of Form II (the water-stable dihydrate), which does not undergo further transformation in suspension and, consequently, does not change in shape or size distribution, thus producing a stable suspension. The second involves the anhydrous Form I (frequently available commercially), provided that adequate measures are taken to prevent the transformation to Form II which results in physical instability. Stabilization of the metastable form (Form I) in aqueous suspension by the use of some formulation additives is the subject of the present report.

The use of various additives to stabilize drug polymorphs has already been reported (2–6). These additives included structurally related compounds, viscosity-imparting materials (hydrocolloids), surfactants, and coloring agents. The present study is concerned with effects of representative examples of these additives, the suspension concentration of Form I, and seeding with Form II on the rate of transformation of the anhydrous succinylsulfathiazole Form I to the dihydrate Form II in aqueous suspension.

EXPERIMENTAL

Materials and Apparatus—Succinylsulfathiazole[1] Forms I and II were obtained as micronized commercial samples. Sulfanilamide, sulfathiazole, phthalylsulfathiazole, methylcellulose, acacia, glycerin, syrup, polysorbate 80, fluorescein sodium, and amaranth, all of USP, BP, or BPC grade, were used. Yellow No. 4[2] and Bordeaux B (BPC 1949) were also used.

IR measurements were made with a double-beam grating spectrophotometer[3].

[1] Courtesy of Chemical Industries Development, Guiza, Egypt.
[2] Lebensmittel, D.F.G., Germany.
[3] Perkin-Elmer model 237-B.

Table I—Effect of Additives on the Rate of Transformation of Succinylsulfathiazole Form I in Aqueous Suspension at 40°

Additive	Concentration, % w/v	Lag Time, min	$K \times 10^4$, min^{-1}
Standard	—	0	40.30
Sulfanilamide	0.1[a]	0	78.75
Sulfathiazole	0.1[a]	90	18.59
Phthalylsulfathiazole	0.1[a]	210	12.55
Glycerin	20[b]	0	65.24
Syrup	50[b]	0	40.30
Acacia	2	0	27.18
Polysorbate 80	1.0	0	103.60
Polysorbate 80	0.5	0	85.42
Polysorbate 80	0.05	0	63.49
Polysorbate 80	0.005	0	40.30
Amaranth	0.005	0	42.42
Yellow No. 4	0.005	0	48.48
Fluorescein sodium	0.005	0	54.53
Bordeaux B	0.005	0	50.30

[a]Corresponding to 10% (w/w) of the total solid succinylsulfathiazole in suspension. [b]Percent v/v.

Methods—Aqueous suspensions of succinylsulfathiazole Form I (1% w/v), each containing a known quantity of one additive, were prepared. The suspensions were kept in a thermostated water bath at 40 ± 0.1°. Samples were withdrawn at various time intervals and filtered, and the concentration of Form I in the solid phase was determined as previously described (1). A temperature of 40° was adopted since, as previously shown (1), transformation was rather slow at room temperature.

Acceleration of the transformation of succinylsulfathiazole Form I, in the presence of phthalylsulfathiazole as an additive, was carried out. For this purpose, 1% (w/v) suspensions of this form, containing 10% (w/w) of phthalylsulfathiazole in succinylsulfathiazole, were kept at 55, 70, and 85 ± 0.1°. The suspensions were assayed periodically for Form I as before.

Seeding experiments were carried out to evaluate the effect of including nuclei of the water-stable succinylsulfathiazole Form II on the rate of transformation of Form I. For this purpose, 5% (w/w) of Form II in Form I was used in place of Form I alone in the presence and absence of some additives.

The effect of the suspension concentration on the rate of transformation of succinylsulfathiazole Form I was studied by measuring the rate in suspensions containing 1, 2, 5, and 10% (w/v) of Form I.

RESULTS AND DISCUSSION

The inhibitory effect of the various additives on the rate of transformation of succinylsulfathiazole Form I, as previously described (6), is manifested by the appearance of a lag period during which the transformation is very slow (almost negligible) and/or obvious rate retardation. The lag period may be interpreted (6) as being a measure of the time needed to produce, through transformation of small particles of Form I, an adequate number of nuclei of the water-stable Form II, which is presumably a prerequisite for the transformation to take place under steady-state conditions (when the various factors affecting the system come to an equilibrium state). Table I summarizes the effect of various additives on the rate of transformation of succinylsulfathiazole Form I in aqueous suspension.

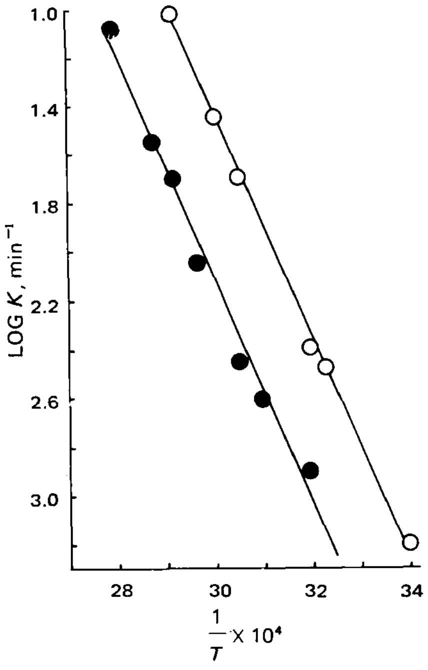

Figure 2—Arrhenius plot of the transformation of succinylsulfathiazole Form I to Form II. Key: ○, standard; and ●, in the presence of 0.1% (w/v) phthalylsulfathiazole.

The effect of structurally related compounds on the rate of transformation of succinylsulfathiazole Form I is shown in Fig. 1. Sulfathiazole and phthalylsulfathiazole showed lag periods of 90 and 210 min, respectively. These compounds, being similar in structure to succinylsulfathiazole, are effective transformation retardants in a manner which is probably related to the ease of fit of their molecules to developing nuclei of the water-stable form (Form II).

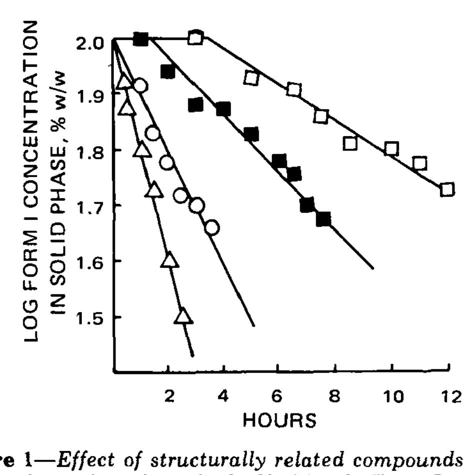

Figure 1—Effect of structurally related compounds on the rate of transformation of succinylsulfathiazole Form I to Form II at 40°. Key: △, sulfanilamide; ○, standard; ■, sulfathiazole; and □, phthalylsulfathiazole.

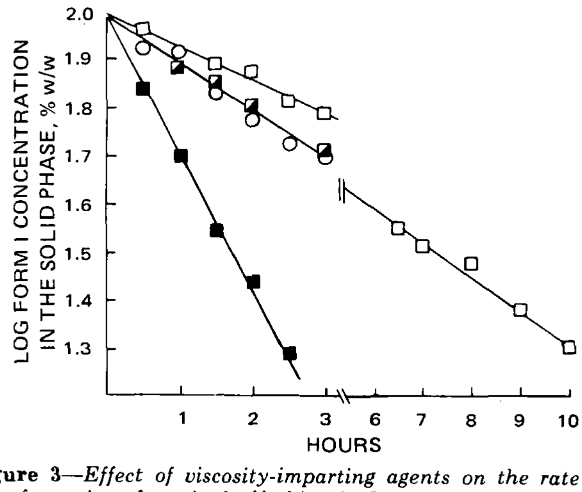

Figure 3—Effect of viscosity-imparting agents on the rate of transformation of succinylsulfathiazole Form I to Form II at 40°. Key: ■, glycerin, 20% (v/v); ○, standard; ◪, syrup, 50% (v/v); and □, acacia, 2% (w/v).

Table II—Kinetic Parameters for the Transformation of Succinylsulfathiazole Form I in the Presence and Absence of Phthalylsulfathiazole in Aqueous Suspension

Additive	Rate Constant $K \times 10^4$, min^{-1}										$t_{1/2}$, $25^{\circ a}$, hr	E_a, kcal/mole
	22°	37°	40°	50°	55°	60°	65°	70°	75°	85°		
Standard[b]	6.3	33.6	40.3	—	203.8	361.8	—	959.4	—	—	13.6	21.1
Phthalylsulfathiazole	—	—	12.6	24.6	35.5	—	87.1	200	282	836	66.4	21.2

[a] Determined by extrapolation. [b] Data from Ref. 1.

Unexpectedly, sulfanilamide increased the rate of transformation of Form I to Form II (Fig. 1). This finding may be interpreted by assuming that sulfanilamide molecules, instead of retarding the transformation rate as with other sulfonamides, probably acts as nuclei for the development of crystals of Form II. The smaller and simpler structure of a sulfanilamide molecule would allow for this behavior. The mechanism of action of structurally related compounds probably involves inhibition of the formation of nuclei of the water-stable form by fitting into developing sites of these nuclei, a mechanism that would require the close similarity of the chemical structure as well as a favorable spatial configuration (7).

Acceleration of the transformation of succinylsulfathiazole Form I to Form II in the presence of phthalylsulfathiazole was carried out at several elevated temperatures, and a comparison of the results with those obtained for a standard suspension of Form I containing no additives is shown in Table II. The Arrhenius plots of the data are shown in Fig. 2. It could be observed from Table II that, although the activation energy calculated from the Arrhenius plot (Fig. 2) of the reaction was not significantly affected by the presence of phthalylsulfathiazole, the half-life at 25° was increased about fivefold and the rate constants for the transformation at all temperatures employed were considerably decreased.

Seeding with nuclei of Form II in aqueous suspensions of succinylsulfathiazole Form I containing sulfathiazole or phthalylsulfathiazole eliminated the lag period, indicating that the lag period is really a measure of the time needed to produce an adequate number of nuclei. However, the transformation rate that followed was not significantly affected (Table III).

The effect of viscosity-imparting materials on retarding the transformation of succinylsulfathiazole Form I is shown in Fig. 3. Methylcellulose, in concentrations ranging from 0.05 to 1% (w/v), inhibited the transformation of Form I for periods of over a year at room temperature. Acacia (2% w/v) retarded the rate of transformation only slightly. Simple syrup (50% v/v) had practically no effect on the rate of transformation. Glycerin (20% v/v), on the other hand, accelerated the transformation rate, probably by improving the wetting and solvation of succinylsulfathiazole Form I in aqueous suspension. The transformation-retarding effect of various viscosity-imparting materials could be related to their suppressive effect on both nuclei formation and solvent-mediated growth of the nuclei formed. This effect is, however, less apparent at higher temperatures.

The effect of polysorbate 80 on the rate of transformation of succinylsulfathiazole Form I to Form II varied with temperature (Fig. 4). At room temperature (≃22°), the rate of transformation decreased about 10 times in the presence of polysorbate 80 (1% w/v). Experiments carried out at a higher temperature (40°), using different concentrations of polysorbate 80 (0.05, 0.5, and 1.0% w/v), showed an increase in the rate of transformation of about twofold. The increase in the transformation rate was found to be directly proportional to the concentration of polysorbate 80.

This behavior might be understood if one considers the opposing effects of a temperature increase and the inclusion of polysorbate 80. Polysorbate 80, at low temperatures, may form an interfacial barrier (6, 8) which retards the transformation rate. However, the increase in the rate of transformation at higher temperatures suggests that the retardation effects are either no longer present or being outweighed by other factors such as a solubilization effect (9, 10). Therefore, it would be expected that higher surfactant concentrations could accelerate the transformation rate at higher temperature conditions.

Coloring agents had a slight transformation-accelerating effect on succinylsulfathiazole Form I (Fig. 5). Coloring agents, because of their slight surface activity, probably improve the wetting of the crystal surfaces, thus accelerating the transformation.

Seeding aqueous suspensions of succinylsulfathiazole Form I with nuclei of the water-stable form (Form II) at various temperatures accelerated the rate of transformation of Form I to Form II. Seeding effects (Table IV and Fig. 6) were more pronounced at lower temperatures. It has already been shown (1) that a temperature increase had a marked transformation-accelerating effect. This entails the formation of a large number of nuclei in a relatively short time. Since, under high temperature conditions, an adequate number of nuclei is available, seeding with more nuclei of the water-stable dihydrate form would only have a slight effect, as shown by the present results.

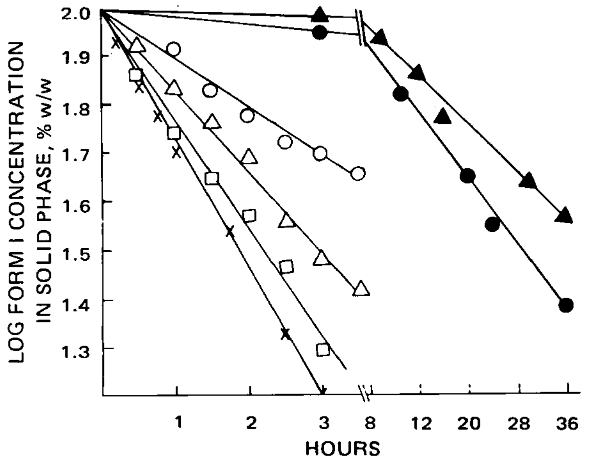

Figure 4—*Effect of polysorbate 80 on the rate of transformation of succinylsulfathiazole Form I to Form II. Key:* □, *0.5% (w/v) polysorbate 80 (40°);* ○, *standard (40°);* ●, *standard (22°);* △, *0.05% (w/v) polysorbate 80 (40°);* ×, *1.0% (w/v) polysorbate 80 (40°); and* ▲, *1% (w/v) polysorbate 80 (22°).*

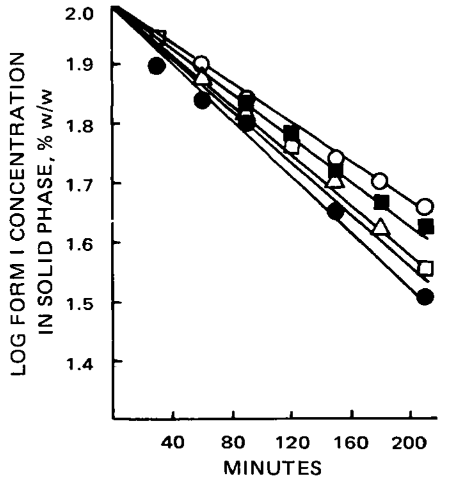

Figure 5—*Effect of coloring agents on the rate of transformation of succinylsulfathiazole Form I to Form II at 40°. Key:* ●, *fluorescein sodium;* □, *Bordeaux B;* △, *Yellow No. 4;* ■, *amaranth; and* ○, *standard.*

Table III—Effect of Seeding on the Rate of Transformation of Succinylsulfathiazole Form I to Form II in the Presence of Sulfathiazole and Phthalylsulfathiazole at 40°

	$K \times 10^4$, min^{-1}	
Additive	Unseeded	Seeded
Standard	40.30	154.44
Sulfathiazole	18.59	18.67
Phthalylsulfathiazole	12.55	13.60

Table IV—Effect of Seeding on the Rate of Transformation of Succinylsulfathiazole Form I to Form II in Aqueous Suspension at Various Temperatures

	$K \times 10^4$, min^{-1}		
Suspension	22°	40°	55°
Standard	6.33	40.30	203.82
Seeded	27.59	154.44	460.60

Seeding effects observed under conditions of the present study are not consistent with those previously reported (6) for sulfameter, where the transformation rate was unaffected by seeding. The discrepancy could be attributed to the rapid rate of transformation of the metastable polymorph of sulfameter ($t_{1/2}$ = 15 min at 25°) relative to the rather slow transformation of succinylsulfathiazole Form I ($t_{1/2}$ = 16 hr at 25°). The rapid rate of transformation in the sulfameter system provides, in a short time, an adequate number of nuclei of the water-stable form, so seeding effects are not apparent. The transformation of succinylsulfathiazole Form I, on the other hand, is accelerated when seeds of Form II are introduced, since the formation of nuclei under standard conditions is rather slow.

The effect of suspension concentration of succinylsulfathiazole Form I on the rate of transformation to Form II is shown in Fig. 7.

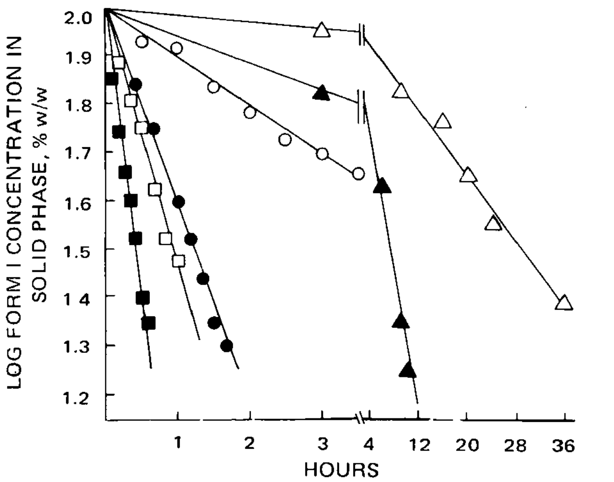

Figure 6—*Effect of seeding with nuclei of Form II on the rate of transformation of succinylsulfathiazole Form I under different temperatures. Key:* □, *55°;* ■, *55° seeded;* ○, *40°;* ●, *40° seeded;* △, *22°; and* ▲, *22° seeded.*

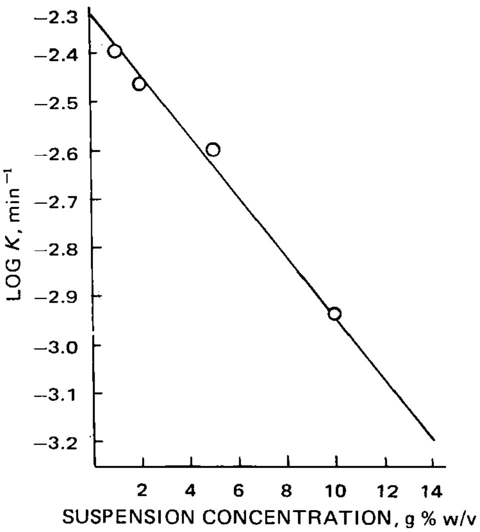

Figure 7—*Effect of suspension concentration of succinylsulfathiazole Form I on the rate of transformation to Form II.*

A linear decrease is observed when the log of the transformation rate constants is plotted against the suspension concentration.

According to the results of the present investigation, assuming the water-stable Form II is not available, the formulation of succinylsulfathiazole Form I in physically stable aqueous pharmaceutical suspensions may be achieved by including a suitable transformation retardant, *e.g.*, methylcellulose. Under these conditions, the suspension would keep its uniformity and ease of resuspension for the expected shelflife of the preparation.

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