Effect of Polyethylene Glycol 4000 on Dissolution Properties of Sulfathiazole Polymorphs

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Abstract □ The dissolution rates of the two polymorphic forms of sulfathiazole containing polyethylene glycol 4000 were significantly different in water. The effect of agitation on the dissolution rates also was studied. At higher stirring speeds, the dissolution rates of the stable form were affected more than the metastable form. A high concentration of polyethylene glycol 4000 seemed to affect the dissolution properties of the metastable polymorph more than the stable polymorph.

Keyphrases □ Polyethylene glycol 4000—effect on dissolution properties of two sulfathiazole polymorphs □ Sulfathiazole—polymorphs, effect of polyethylene glycol 4000 on dissolution properties □ Dissolution—sulfathiazole polymorphs, effect of polyethylene glycol 4000

The pharmaceutical and biological aspects of polymorphism have been elaborated in detail (1). Generally, the high energy or metastable polymorphs show higher dissolution rates than the stable form, except in instances where the conversion of metastable to stable forms is extremely rapid in the solvent medium (2, 3). This conversion was reported for sulfathiazole, which exists in at least two polymorphic forms (3).

The purpose of this paper is to demonstrate significant differences in the dissolution rates of sulfathiazole polymorphs in water when combined with polyethylene glycol 4000. The effects of agitation and the percent composition of polyethylene glycol 4000 are also discussed.

EXPERIMENTAL

Material—Sulfathiazole[1] and polyethylene glycol 4000[2] were obtained commercially.

Preparation and Identification of Polymorphs—The commercially supplied sulfathiazole was form I. Form II was prepared by a thermal method (4, 5) by heating form I in an oven at 175° for 20 min. The polymorphic forms were confirmed using a differential thermal analyzer[3]. The use of thermal analysis was shown to correspond well with the X-ray diffraction spectrum (5). Figure 1 shows the thermograms for both forms I and II.

Preparation of Physical Mixtures—Both sulfathiazole and polyethylene glycol 4000 were passed through a 200-mesh sieve and mixed to give 2, 5, and 10% (w/w) composition of polyethylene glycol 4000. These physical mixtures were then mixed in a drum-type mixer, using 30-ml (1-oz) plastic vials mounted at a 45° angle to a variable speed motor. Each sample was mixed for 30 min at 30 rpm, with occasional tapping of the vial with a spatula to avoid any aggregation on the vial wall.

Dissolution Rate Studies—Dissolution rates were determined using constant-surface tablets made by compressing 300 mg of physical mixture in a press[4] at 3178 kg (7000 lb) of pressure. These tablets were then mounted with a commercial cement[5] in a tablet holder to expose a surface area of 1.327 cm^2, and the tablet holders were attached to a variable speed motor. The dissolution studies were performed in 500 ml of distilled water thermostatically controlled at 25 ± 0.1°.

The absorbance of the solution was monitored using a continuous-flow assembly at 283 nm through a spectrophotometer[6]. The dissolution of each tablet was determined at 42, 96, 126, and 216 rpm in the order of both increasing and decreasing speed. In all instances, at least duplicate measurements were made and a high degree of reproducibility was achieved.

RESULTS AND DISCUSSION

The dissolution rates of the two polymorphs of sulfathiazole were obtained from constant-surface tablets, containing 2, 5, or 10% polyethylene glycol 4000, by linear regression of the amount dissolved *versus* time data from the linear parts of the plots. In all instances, the r^2 value was greater than 0.99. The differences between the dissolution rates of the two polymorphs and of each polymorph at different polyethylene glycol 4000 compositions were always significant at the 95% confidence level.

Effect of Polyethylene Glycol 4000—It has been shown (6) that the addition of high molecular weight, water-soluble polymers can increase the dissolution rates of poorly water-soluble drugs. Figure 2 shows the dissolution rates of sulfathiazole form I containing different proportions of polyethylene glycol 4000.

The addition of polyethylene glycol 4000 as a physical mixture clearly increased the dissolution rate of sulfathiazole. Comparisons with the dissolution rates of pure sulfathiazole were not made, however, since the pure compound offered great resistance to compression in a tablet form at the low compression pressures used to avoid any complexities due to polymorphic transition or glass formation (5–7) at high compression pressures. The tablets made at 3178 kg (7000 lb) of pressure showed no polymorphic transition or glass formation, as indicated by differential thermal analysis of compressed samples.

Effect of Stirring Speed—The dissolution rates were deter-

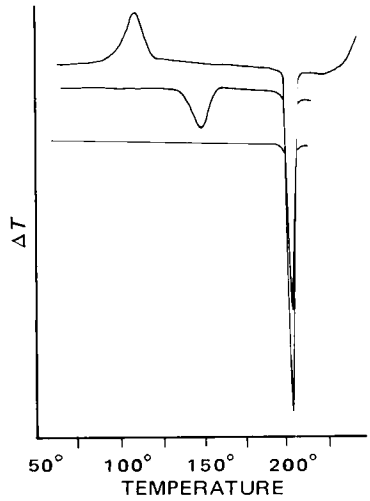

Figure 1—*Differential thermal analysis thermograms of sulfathiazole. Key: bottom, sulfathiazole form II; middle, sulfathiazole form I; and top, rerun of sulfathiazole form I sample heated to 215° and cooled to ambient temperature. The exothermic peak indicates the conversion of amorphous to crystalline form. All runs were obtained at a heating rate of 10°/min.*

[1] Eli Lilly & Co., Indianapolis, Ind.
[2] Pluracol E-4000, BASF Wyandotte Corp., Wyandotte, Mich.
[3] DuPont 990, E. I. du Pont de Nemours & Co., Wilmington, Del.
[4] Loomis Engineering & Manufacturing Co., Caldwell, N.J.
[5] Duco Cement, E. I. du Pont de Nemours & Co., Wilmington, Del.
[6] Beckman DB-G, Beckman Instrument Co., Fullerton, Calif.

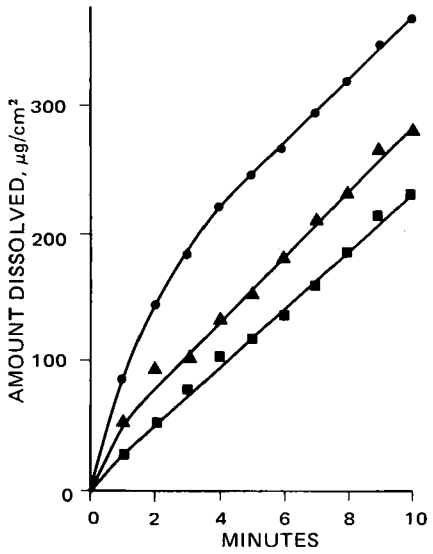

Figure 2—*Dissolution rates of sulfathiazole form I–polyethylene glycol 4000 physical mixtures. Key (polyethylene glycol 4000): ●, 10%; ▲, 5%; and ■, 2%.*

mined at 42, 96, 126, and 216 rpm to study the effect of diffusion layer thickness around the constant-surface tablets. As shown in Fig. 3, the dissolution rates invariably increased with the stirring speed. The slopes in Fig. 3 representing the change of dissolution rate with respect to the stirring speed are much steeper at low stirring speeds, indicating that the diffusion layer thickness indeed is a rate-limiting step. At high stirring speeds, the slopes decreased, indicating a smaller contribution of the diffusion layer thickness in determining the dissolution rates.

Effect of Polymorphism—The dissolution rates of the two polymorphs of sulfathiazole were reported to be indistinguishable in water and in water–ethanol mixtures containing up to 25% (v/v) ethanol (3). It was suggested that this result was due to the extremely rapid conversion of form II to form I in these solvents. In the present study, a highly significant difference was observed between the dissolution rates of the two polymorphs when polyethylene glycol 4000 was added to the formulation.

Figure 3 shows the dissolution rates of the two polymorphs from formulations containing different proportions of polyethylene glycol 4000 at different stirring speeds. In all instances, sulfathiazole form II showed a higher dissolution in water than did form I. The data presented here allow some interesting observations. For example, the ratio of the dissolution rates of forms II and I changed with the stirring speed (Fig. 4). At speeds above 96 rpm, the increase in the dissolution rate of form II was invariably less than that of form I. This finding can be explained on the basis of the

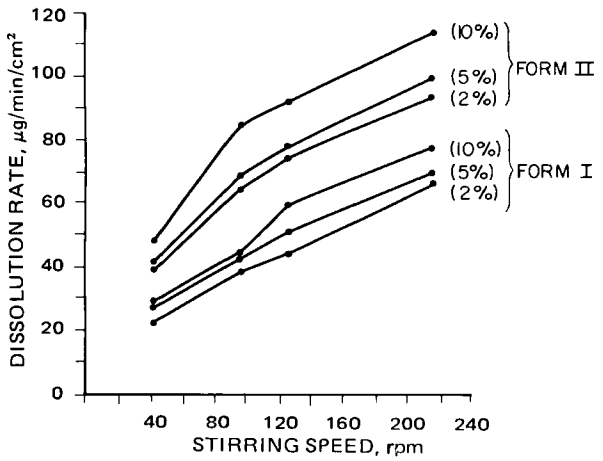

Figure 3—*Dissolution rates of sulfathiazole polymorphs containing different proportions of polyethylene glycol 4000 as a function of stirring speed.*

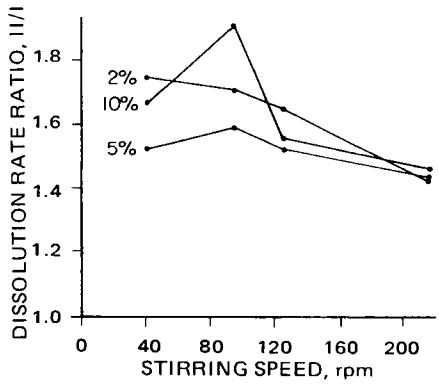

Figure 4—*Relationship between the dissolution rate ratios of the two sulfathiazole polymorphs and the stirring speed at different percentage compositions of polyethylene glycol 4000.*

diffusion layer thickness and the chemical potential of the two polymorphic forms. Since form I has lower solubility than form II (7), a decrease in the diffusion layer thickness will result in a greater increase in the dissolution rate of form I compared to form II (6).

At low stirring speeds where the diffusion layer thickness was large, the relationships were more complicated. The addition of polyethylene glycol 4000 significantly affected the surface properties; but at low percentage composition of polyethylene glycol 4000, *e.g.*, 2%, the effect on the surface property was minimal. As shown in Fig. 4, the ratio of the dissolution rates at the lowest stirring speed (42 rpm) was 1.75, which is in agreement with the solubility ratios of these polymorphs (3, 8). The high percentage compositions of polyethylene glycol 4000 showed a lower dissolution rate ratio at 42 rpm.

A similar argument as already presented can be developed here: that the dissolution rate of sulfathiazole form I having lower solubility is affected more due to the inclusion of the hydrophilic polyethylene glycol 4000 than is form II. As the stirring speed increased from 42 to 96 rpm, a dramatic increase in the dissolution rate ratio was observed, the magnitude of which was proportional to the percentage composition of polyethylene glycol 4000. The 10% compositon showed a much larger increase than the 5% composition, and the 2% composition showed a decrease in the ratio. These observations are difficult to explain, but some speculation can be made.

At the intermediate diffusion layer thickness, as the speed increased from 42 to 96 rpm, the effect of the polyethylene glycol 4000 interaction became more significant, possibly by increasing the diffusion of the solute molecules through the diffusion layer or by increasing the solubility in this layer. This aspect was further reflected in higher ratios of dissolution for the two polymorphs with 10% polyethylene glycol 4000 compared to 5% at all stirring speeds.

Therefore, the presence of polyethylene glycol 4000 significantly

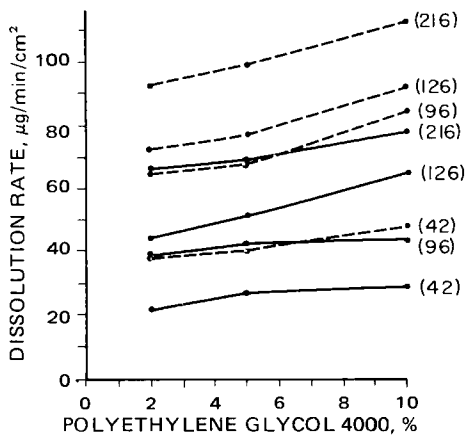

Figure 5—*Dissolution rates of sulfathiazole as a function of polyethylene glycol composition at different stirring speeds. Key: —, form I; and - - -, form II.*

affects the dissolution rate relationship as a function of diffusion layer thickness. Figure 5 shows the dissolution rates plotted as a function of the polyethylene glycol 4000 percentage composition. An interesting observation that can be made from this plot is that as the percentage of polyethylene glycol 4000 increased from 2 to 5%, the increase in the dissolution rates of form I was higher compared to form II for all stirring speeds except the highest speed of 216 rpm. However, as the percentage increased from 5 to 10%, the relationship was inversed, showing a greater increase in the dissolution rate of form II compared to form I at all stirring speeds.

This analysis further strengthens the postulate that at low percentage composition of polyethylene glycol 4000, the surface property changes affect the dissolution rates of form I more than of form II, but the dissolution rates of form II are affected more than those of form I at high percentage compositions.

These observations clearly show that the dissolution rates of the two sulfathiazole polymorphs can differ significantly even if small amounts of additive such as polyethylene glycol 4000 are added. Furthermore, the comparisons of dissolution rates should be made in conjunction with reference to the diffusion layer thickness since the mechanism of dissolution appears to be highly dependent on this factor.

The study presented here also shows that there is no significant conversion of form II to form I in water in the presence of polyethylene glycol 4000. The bioavailability aspects of these findings will be reported later.

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Selenium Heterocycles XVIII: Synthesis and Antibacterial Activity of 4-Substituted (1,2,3-Selenadiazol-5-yl)carbamic Acid Esters and Their Sulfur Analogs

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Abstract □ 4-Substituted (1,2,3-selenadiazol-5-yl)carbamic acid esters and their sulfur analogs were prepared from the Curtius rearrangement of the corresponding carboxazides. None of the compounds showed significant antibacterial activity.

Keyphrases □ Selenium heterocycles—synthesis and antibacterial activity of 4-substituted (1,2,3-selenadiazol-5-yl)carbamic acid esters and sulfur analogs □ Sulfur heterocycles—synthesis and antibacterial activity of 4-substituted (1,2,3-thiadiazol-5-yl)carbamic acid esters and selenium analogs □ Antibacterial agents, potential—4-substituted (1,2,3-selenadiazol-5-yl)carbamic acid esters and sulfur analogs

It has been reported that 1,3,4-thiadiazolylcarbamic acid esters have significant antiviral activity (1). These compounds and 1,3,4-selenadiazolylcarbamic acid esters showed antibacterial efficacy (2, 3). 1,2,3-Thiadiazole derivatives of benzimidazole, benzoxazole, and benzothiazole were reported as anthelmintics (4). Some phosphorus compounds having the 1,2,3-thiadiazole ring system showed insecticide activity (5), and 4-amino-1,2,3-thiadiazolesulfonamides exhibited antibacterial properties (6). In a continuing effort to find antiviral and antimicrobial agents, 4-substituted (1,2,3-selenadiazol-5-yl)carbamic acid esters and their sulfur analogs were prepared and their efficacy was determined.

DISCUSSION

Chemistry—4-Substituted 1,2,3-thiadiazole-5-carboxylic acid ethyl esters were prepared by an oxidative cyclization of methyl or methylene ketone semicarbazones with thionyl chloride (7).

4-Substituted 1,2,3-selenadiazole-5-carboxylic acid ethyl esters were prepared following the general method reported previously (8) (Scheme I).

1,2,3-Thiadiazole-5-carboxazides and their selenium analogs were prepared by two independent methods. In Method A, the appropriate ester was hydrolyzed to the carboxylic acid and the carboxazide was prepared with thionyl chloride and sodium azide (Scheme II). In Method B, the ester was reacted with hydrazine hydrate and the corresponding hydrazide was then transformed to the carboxazide by reaction with sodium nitrite in acetic acid (9) (Scheme III).

Curtius rearrangement of the azides was readily achieved in alcohols (Schemes II and III). Although 1,2,3-selenadiazole is unstable at 170–180° and decomposes to give acetylene (8), it is quite stable under the conditions used in this work for the Curtius rearrangement.

The physical data for the prepared compounds are summarized in Table I.

Microbiological Evaluation—All compounds listed in Table I were tested against *Bacillus subtilis* (NCTC 3610), *Staphylococ-*