Enhancement of Dissolution Rates of Poorly Water-Soluble Drugs by Crystallization in Aqueous Surfactant Solutions I: Sulfathiazole, Prednisone, and Chloramphenicol

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Abstract □ Effects of crystallization of poorly water-soluble drugs in aqueous surfactant solutions on *in vitro* dissolution rates were investigated. Marked enhancement was observed for chloramphenicol, sulfathiazole, and prednisone. Differential thermal analysis studies indicated the presence of small amounts of surfactant in surfactant-treated crystals. Possible mechanisms of dissolution enhancement are discussed.

Keyphrases □ Dissolution rates—chloramphenicol, sulfathiazole, prednisone, effect of crystallization in aqueous surfactant solutions □ Chloramphenicol—dissolution rate, effect of crystallization in aqueous surfactant solutions □ Sulfathiazole—dissolution rate, effect of crystallization in aqueous surfactant solutions □ Prednisone—dissolution rate, effect of crystallization in aqueous surfactant solutions □ Surfactants, aqueous—crystallization of chloramphenicol, sulfathiazole, and prednisone in polysorbate 80, effect on dissolution rates

Many methods have been used to enhance dissolution rates of poorly water-soluble or insoluble drugs. The methods include, for example, salt and polymorphic formation (1); micronization, microcrystallization, solid dispersion, and coprecipitation using inert, water-soluble compounds as carriers (2–6); and grinding with (7), and adsorption onto (8), an inert water-insoluble compound.

The purpose of this article is to report the preliminary findings of another unique method to enhance the dissolution rate of poorly water-soluble or insoluble drugs. The basic method simply involves the recrystallization of the drug in an aqueous surfactant solution. Three drugs will be used for illustration.

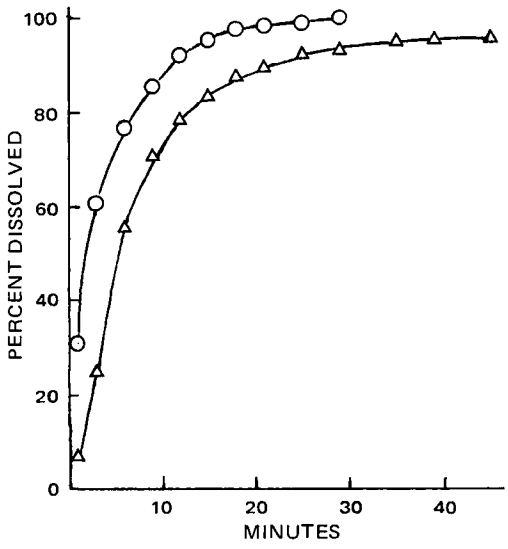

Figure 1—*Average percent of sulfathiazole dissolved as a function of time. Key: △, control; and ○, surfactant treated.*

Table I—Average Time (Minutes) for 50% of Drug to Dissolve during the Dissolution Study

Drug	Crystallization in Absence of Surfactant	Crystallization in Presence of Surfactant
Prednisone	9	2
Sulfathiazole	6	2
Chloramphenicol	2	<1

EXPERIMENTAL

Materials—Chloramphenicol[1], sulfathiazole[2], and prednisone[3] were obtained from commercial sources and used without further purification.

Method of Crystallization—A certain amount of drug powder was initially dissolved in a small volume of a water-miscible organic solvent at ambient temperature. The drug precipitated after this solution was diluted with an equal volume of water or 2.5% aqueous solution of polysorbate 80[4] kept at about 0° in a water bath. The precipitated crystals were immediately collected by filtration and dried in a desiccator. They were pulverized with a mortar and pestle, and the 80–100-mesh portion after sieving was collected for the dissolution study.

The volumes of the water-miscible solvents or solvent system used to dissolve the drugs were 14 ml of ethanol for 2 g of chloramphenicol, 9 ml of dimethylformamide[5] for 8 g of sulfathiazole, and a mixture of 30 ml of ethanol and 50 ml of methanol for 1 g of prednisone.

Dissolution Studies—The dissolution studies were conducted in water at 37° by the beaker method (9). A three-blade, 4.4-cm (1.75-in.)

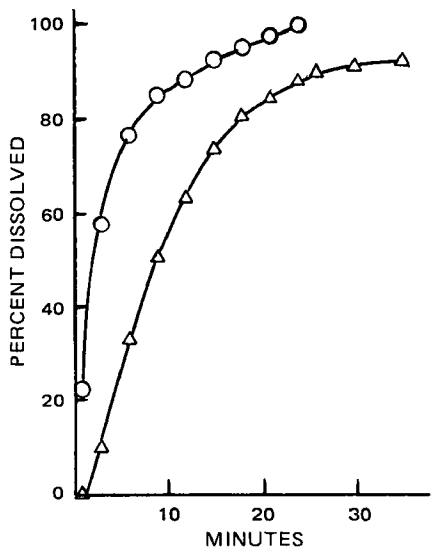

Figure 2—*Average percent of prednisone dissolved as a function of time. Key: △ control; and ○, surfactant treated.*

[1] Parke, Davis & Co., Detroit, Mich.
[2] Merck Sharp & Dohme Research Laboratories, West Point, Pa.
[3] Schering Corp., Bloomfield, N.J.
[4] Tween 80, Atlas Powder Co., Chicago, Ill.
[5] J. T. Baker Chemical Co., Phillipsburg, N.J.

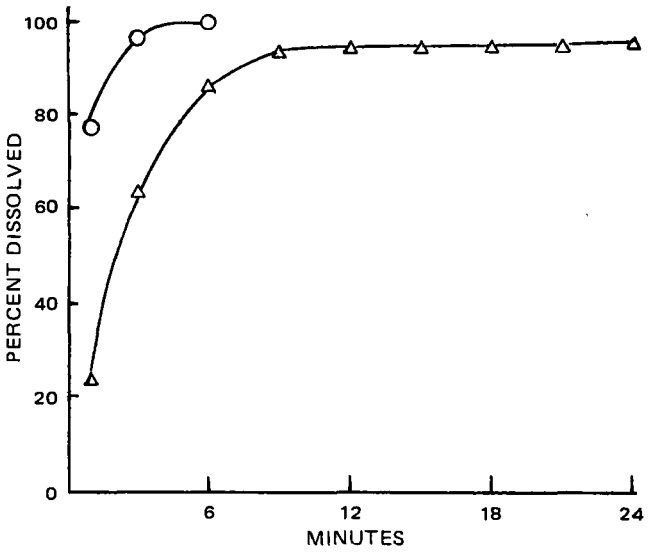

Figure 3—*Average percent of chloramphenicol dissolved as a function of time. Key: Δ, control; and O, surfactant treated.*

stirrer[6] with a stirring rate of 50 rpm was employed. The drug powder was spread onto the surface of the dissolution medium, and the amount of drug dissolved was analyzed directly after filtration by a spectrophotometric method. The wavelengths used were 278, 320, and 238 nm for chloramphenicol, sulfathiazole, and prednisone, respectively. The amounts of drug used were 25, 50, and 5 mg, respectively.

For sulfathiazole, 1 liter of the dissolution medium was used; for the other two drugs, only 500 ml was used. Four dissolution studies were performed on each type of crystal preparation. The Student *t* test was employed for the statistical analysis.

Differential Thermal Analysis—Powders of each drug, prepared in the absence or presence of the surfactant, were studied with a differential thermal analyzer[7] (3–5). A heating rate of 20°/min was used.

RESULTS AND DISCUSSION

The results of the dissolution studies, expressed in terms of percent dissolved as a function of time for the three drugs, are shown in Figs. 1–3. Due to the high reproducibility of the dissolution study, the data on standard errors are not shown in the figures. During the first few minutes of study, the dissolution rates of crystals prepared in the presence of the surfactant were all significantly higher (*e.g.*, $p < 0.005$ for prednisone up to 9 min, $p < 0.01$ for sulfathiazole up to 6 min, and $p < 0.001$ for chloramphenicol up to 6 min). Times estimated for the 50% dissolution for the three drugs are summarized in Table I.

The mechanisms of dissolution rate enhancement by this unique crystallization method are not discussed fully in this preliminary report. The results of the differential thermal analysis studies (Figs. 4 and 5) indicate that the presence of the surfactant during the crystallization process did not result in a different polymorphic form. The depression of final melting points by approximately 0.5–1.0° for all three surfactant-treated drugs strongly suggests the presence of a small amount of surfactant in these crystals.

Some surfactant molecules, due to their surface activity, might be adsorbed onto the hydrophobic surface of the crystals. This adsorption would undoubtedly increase the wettability of the powder or crystals and thereby increase their dissolution rate (2). The presence of the surfactant during the crystallization process might also cause a defect in the crystal structure and the crystal would become thermodynamically unstable and, hence, dissolve faster. The possibility of the formation of a solid solution of the water-soluble surfactant in the drug crystal might also enhance the dissolution (2).

Although it has been shown that surfactants can increase the solubility of poorly soluble compounds (10), the amount of the surfactant present in the crystals studied in the present investigation was probably too negligible to affect the solubility of the drug in bulk solution. However, the surfactant, present inside and/or outside of the crystals, might enhance the solubility of a drug in the diffusion layer during the dissolution process.

The effects of concentration and types of surfactants on the extent of dissolution rate enhancement, together with the nature of the surfactant present in the crystal, are currently being investigated in this laboratory.

Although only three drugs were studied, it is believed that such an approach can be applied to many poorly water-soluble or insoluble drugs.

[6] Nalgene stirrer, Fisher Scientific Co., Skokie, Ill.
[7] Model 990, E. I. du Pont de Nemours & Co., Wilmington, Del.

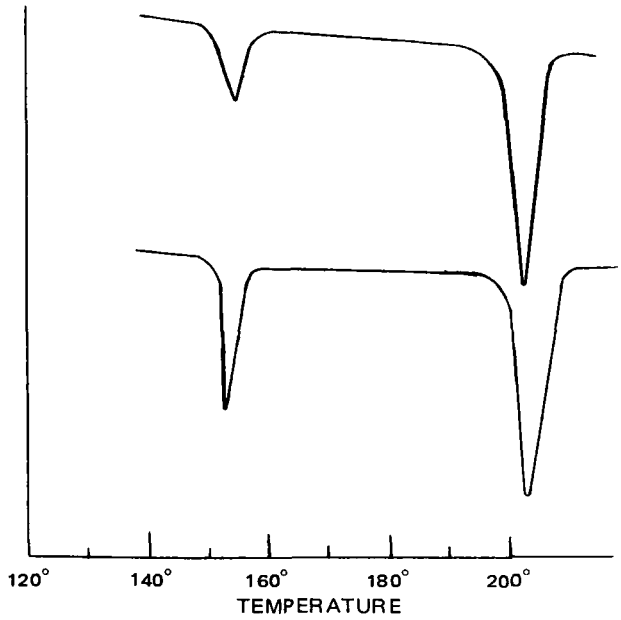

Figure 4—*Differential thermal analysis thermograms of sulfathiazole. Key: top, surfactant treated; and bottom, control.*

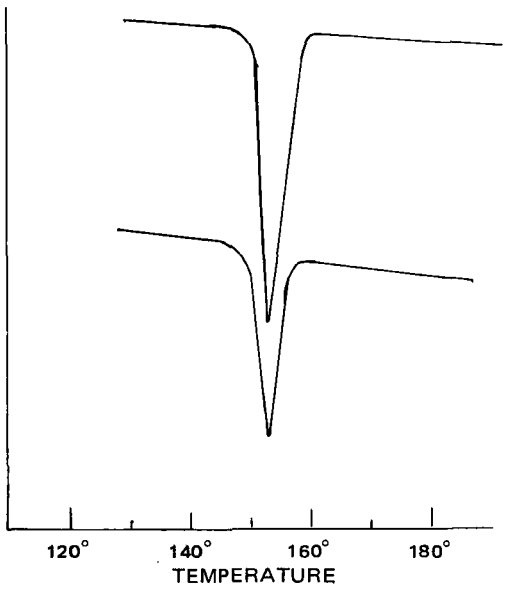

Figure 5—*Differential thermal analysis thermograms of chloramphenicol. Key: top, control; and bottom, surfactant treated.*

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Molecular Orbital Studies of Antischistosomal Agents

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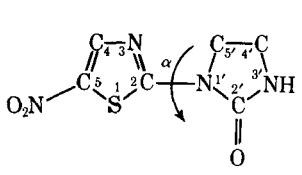
Abstract □ Molecular orbital calculations were used to investigate the antischistosomal agent, niridazole, and an inactive derivative, 1-(5-nitro-2-thiazolyl)-2-ethylurea. The CNDO/2 calculations revealed that the inactive derivative had a preferred conformation stabilized by an intramolecular hydrogen bond. The molecular profile, the relative three-dimensional arrangement of constituent atoms, of the inactive derivative was different than that of the niridazole compound. The likelihood of similar intramolecular interactions rendering niridazole derivatives inactive is discussed. The results of the calculations suggest select structural modifications that might increase the efficacy of niridazole derivatives.

Keyphrases □ Niridazole and derivative—preferred molecular conformations, effect on biological activity □ Molecular orbital calculations—preferred conformations of niridazole and derivative □ Structure–activity relationships—niridazole and derivative, preferred molecular conformations, effect on biological activity □ Antischistosomal agents—niridazole, preferred molecular conformation, effect on biological activity

Recent studies concerning the structure–activity relationships of antischistosomal agents revealed certain essential molecular features necessary for activity insofar as nitroheterocyclic compounds of the niridazole (I) type are concerned. One study (1) showed that the activity of niridazole was dependent upon the presence of the nitro and sulfuryl moieties and that the presence of a nonpolar side chain was necessary. This work was definitive and covered many structural variants.

However, one feature that remains unaccounted for is the inactivity of niridazole derivatives in which the imidazolidinone ring is ruptured at the N-1′–C-5′-position. Thus, 1-(5-nitro-2-thiazolyl)-2-ethylurea (II) possesses no antischistosomal activity. The potential importance of a biologically preferred conformation was noted previously (1) and, because of the increased lability of ureido side chain over the imidazolidinone ring, the conformational differences were studied using the molecular orbital approach.



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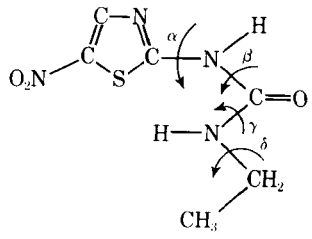
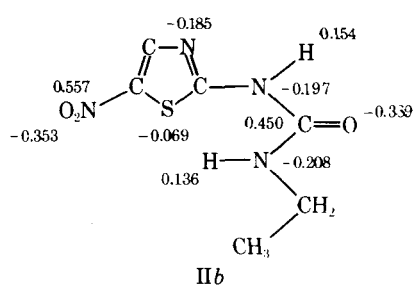


IIa



IIb

EXPERIMENTAL

A series of semiempirical molecular orbital calculations was performed to determine the preferred conformations of the active niridazole compound and its inactive derivative. The Complete Neglect of Differential Overlap (CNDO/2) molecular orbital technique was used for this purpose. The CNDO/2 method assumes that two center overlap integrals are zero, greatly simplifying the Hamiltonian matrix. The success of the method, providing that proper parameterization is used, has been well documented (2–4).

The CNDO/2 method has been used to compute stabilization energies for hydrogen-bonded systems as well as barriers to internal rotation (5, 6). Because of certain limitations concerning the CNDO/2 method, an *ab initio* approach may be preferable. Hydrogen bond energies are usually overestimated while internal barriers to rotation are underestimated. However, with a clear understanding of the method's limitations, one should, in principle, be able to compute potential surfaces in which intramolecular hydrogen bonding plays

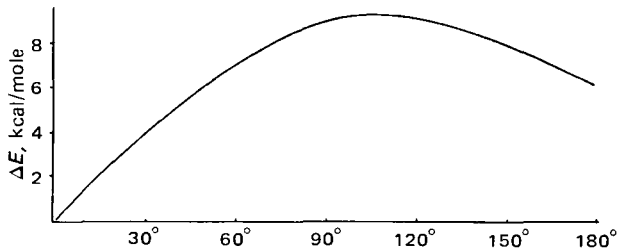


Figure 1—*Potential energy contour for the α-rotomer in niridazole. Energies are plotted relative to the lowest energy conformation, α = 0°.*