(16) R. Kaur, D. J. W. Grant, and T. Eaves, *J. Pharm. Pharmacol.*, **31S**, 48P (1978).
(17) "British Pharmacopoeia," Her Majesty's Stationery Office, London, England, 1973, p. A-128.
(18) R. J. Withey and A. J. Bowker, *J. Pharm. Pharmacol.*, **24**, 345 (1972).
(19) M. Kuhnert-Brandstätter, "Thermomicroscopy in the Analysis of Pharmaceuticals," Pergamon, Oxford, England, 1971, p. 128.
(20) D. L. Simmons, R. J. Ranz, N. D. Gyanchandani, and P. Picotte, *Can. J. Pharm. Sci.*, **7**, 121 (1972).
(21) A. Burger, *Sci. Pharm.*, **43**, 161 (1975).
(22) A. Burger and R. Ramberger, *Mikrochim. Acta*, **II**, 273 (1979).
(23) A. Ebian, M. Moustafa, S. Khalil, and M. Motawi, *J. Pharm. Pharmacol.*, **25**, 13 (1973).
(24) S. T. Bowden, "The Phase Rule and Phase Reactions: Theoretical and Practical," Macmillan, London, England, 1938, p. 153.
(25) K. Sekiguchi, N. Obi, and Y. Ueda, *Chem. Pharm. Bull.*, **12**, 134 (1964).
(26) A. H. Goldberg, M. Gibaldi, and J. L. Kanig, *J. Pharm. Sci.*, **55**, 482, 487 (1966).
(27) W. L. Chiou and S. Niazi, *ibid.*, **62**, 498 (1973).
(28) M. P. Summers and R. P. Enever, *ibid.*, **66**, 825 (1977).
(29) S. A. Said, H. M. El-Fatatry, and A. Sh. Geneidi, *Aust. J. Pharm. Sci.*, **NS3**, 42 (1974).

Comparison of Polyethylene Glycol and Polyoxyethylene Stearate as Excipients for Solid Dispersion Systems of Griseofulvin and Tolbutamide II: Dissolution and Solubility Studies

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Abstract □ The effects of joining a long-chain ester group with the polyethylene glycol molecule were studied in solid dispersion systems by comparing the dissolution and solution properties of such systems prepared from polyethylene glycol 2000 with those prepared from the nontoxic, water-soluble, solid excipient polyoxyethylene 40 stearate. Solid dispersion systems of griseofulvin and tolbutamide were prepared by physical mixing, fusion, or coprecipitation from ethanol. The compacted dispersion systems dissolved by progressive erosion, releasing floccules of microcrystals. The released microcrystals of tolbutamide (3–10 μm) were smaller than the original drug particles (~20 μm), but those of griseofulvin were of similar size to the original particles. In general, the rate and extent of release of each drug were greater from polyoxyethylene 40 stearate than from polyethylene glycol 2000 dispersions. The aqueous solubility and dissolution rate of nondisintegrating disks of each pure drug increased only slightly in the presence of polyethylene glycol 2000 but increased considerably with increasing concentration of polyoxyethylene 40 stearate due to micellar solubilization. Thus, polyoxyethylene 40 stearate generally is superior to polyethylene glycol 2000 in promoting the dispersion of the drugs in solids, disintegration of the compacted solids, and solubilization of the drugs during dissolution.

Keyphrases □ Excipients—polyethylene glycol and polyoxyethylene stearate, comparison as excipients for solid dispersion systems of griseofulvin and tolbutamide, dissolution and solubility studies □ Polyethylene glycol—comparison with polyoxyethylene stearate as excipient for solid dispersion systems of griseofulvin and tolbutamide, dissolution and solubility studies □ Polyoxyethylene stearate—comparison with polyethylene glycol as excipient for solid dispersion systems of griseofulvin and tolbutamide, dissolution and solubility studies

Solid dispersion systems may provide a means of increasing the dissolution rate and improving the bioavailability of drugs that are poorly soluble in water (1, 2). Polyethylene glycol has proven to be a valuable water-soluble matrix material for dispersion systems. In particular, the dissolution rate and bioavailability of griseofulvin from polyethylene glycol dispersions are greater than those of the micronized or microcrystalline drug (2). Chiou (3) recently showed that griseofulvin has negligible or very limited solid solubility in polyethylene glycol dispersion systems, a fact supported by phase equilibrium diagrams (4). Chiou (3) suggested that the marked enhancement of the dissolution and absorption rates of griseofulvin dispersed in polyethylene glycol primarily is a result of the reduced size of the griseofulvin crystals. However, other factors, such as increased wettability, solubilization of the drug by the carrier at the diffusion layer, and the reduction or absence of aggregation and agglomeration, also may contribute.

The formation of solid dispersions of tolbutamide in polyethylene glycol polymers also increased the dissolution rate of this drug, an effect that has been attributed to the formation of a solid solution, the dispersion of the drug in a fine state of subdivision, or improved wetting of the drug particles (5). However, in previous studies in these laboratories (4), solid solution formation was not found.

BACKGROUND

Esterification of polyethylene glycol (I) with a long-chain *n*-acyl residue such as stearate to form polyoxyethylene stearate, for example, produces a nontoxic (6), surface-active macromolecule, which may be a better excipient in dispersion systems than the non-surface-active material, I. This hypothesis is being tested by comparing the properties of dispersion systems of the poorly water-soluble drugs griseofulvin and tolbutamide in polyoxyethylene 40 stearate (II) with those in I. A previous report (4) showed no evidence of solid solution formation, even with II (<1% drug). Tolbutamide was more soluble in II than in I at the same temperature, but griseofulvin showed similar solubility in each liquid excipient. Griseofulvin with either II or I and tolbutamide with I gave monotectic systems, which may be considered as eutectic systems where the eutectic composition is pure griseofulvin or pure tolbutamide. Tolbutamide with

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II gave a eutectic system for which II completely dissolved up to 20% of the tolbutamide.

Compound II is a surface-active agent with a critical micelle concentration in water of 0.014% (w/v); I is not surface active. Surface activity has long been recognized as a potent factor in enhancing dissolution and absorption rates. For example, the addition of a surfactant, *e.g.*, cetomacrogol or lysolecithin, to the dissolution medium increases the dissolution rate of sparingly soluble drugs, such as griseofulvin (7, 8), by micellar solubilization and improved wettability. Furthermore, the addition of aqueous surfactants during recrystallization increases the *in vitro* dissolution of drugs that are poorly soluble in water (9). Since the amount of surfactant released is insufficient to increase significantly the solubility of the drug in the bulk solution, the presence of the surfactant within and outside the crystals might increase the solubility of the drug in the diffusion layer during dissolution.

The objective of the present study was to probe the advantages, if any, of II over I as an excipient for solid dispersion systems of drugs that are poorly soluble in water. The drugs studied were griseofulvin and tolbutamide. *In vitro* release rates of the drug and the contributing processes are compared, and attempts are made to ascertain which factors are involved. A preliminary account of this work was published previously (10).

EXPERIMENTAL

Materials—The following materials and drugs were of food or pharmaceutical grade and were used as supplied: polyoxyethylene 40 stearate[1] (II), polyethylene glycol 2000[2] (I), griseofulvin[2], and tolbutamide[2]. Ethanol (95%) was spectroscopic grade. The pH 7 buffer was phosphate buffer BP (11). The pH 1 buffer was 0.1 *M* HCl. All water was double distilled from an all-glass still.

Preparation of Dispersion Systems—Physical mixtures, fused mixtures, and coprecipitated mixtures of griseofulvin or tolbutamide with I or II were prepared as described previously (4).

Preparation of Solid Compacts—Nondisintegrating disks contained 250 g of powdered griseofulvin or tolbutamide. For griseofulvin, it was necessary to grind up the first disks prepared and to recompress the powder, because the initial compression produced flaky or fragile disks. Disintegrating disks contained 1 g of the dispersion system consisting of the drug and the excipient. The disks (13 mm in diameter) were prepared by compression of powdered materials under vacuum for 5 min in a die[3] assembly for preparing potassium bromide disks for IR spectrophotometry. The load was 10 tons for nondisintegrating disks and 1 ton for disintegrating disks, corresponding to compaction pressures of 739 and 73.9 MN/m^2, respectively. To prevent the dispersion systems from sticking to the platen and anvil in the die, small pieces of greaseproof paper, used for interleaving membrane filters, were placed between each metal surface and the dispersion system.

Dissolution Rate Determination—A modified beaker–stirrer method was employed (12). The Pyrex glass beaker had an internal diameter of 13.8 cm, a height of 20.2 cm, and a capacity of 3 liters. The compact was secured to the center of the base of the beaker with a thin film of silicon paste, and 2 liters of dissolution medium was added. The stirrer motor[4], rotating at 300 rpm, drove a stirrer blade (0.5 × 2.4 cm), which was centrally placed 5 cm above the base of the beaker. Samples (4 ml) were withdrawn by a syringe fitted with a membrane filter[5] (pore diameter 0.45 μm) and were analyzed by UV spectrophotometry[6] at 296 nm for griseofulvin and 228 nm for tolbutamide. The volumes withdrawn were not replaced. For this system, the absorbance values of I and II at the concentrations released were negligible at the λ_{max} values for griseofulvin and tolbutamide. The dissolution profiles were repeated and good agreement was found. Each point reported is the mean of at least two determinations.

Solubility Measurements—The solubility of each drug in aqueous solution at 37° was determined by shaking an excess of powdered drug with the solvent, sampling the solution by means of a calibrated plastic syringe fitted with a membrane filter[5] (pore diameter 0.45 μm), diluting the sample quantitatively, and determining the absorbance by UV spectrophotometry[6] at the λ_{max} values. Two equilibration procedures were compared. In the first procedure, equilibration was achieved by shaking the solutions in a water bath at 37° for 3 and 5 days. Identical results after each period indicated that equilibrium had been attained. In the second procedure, the solid drug was shaken with the solvent in a water bath at 45° for 4 hr and then at 37° for 24 hr. Both methods of equilibration gave identical results. Based on this finding, the second method was adopted, because it was quicker and less liable to permit decomposition of the dissolved drug or the dissolved excipient.

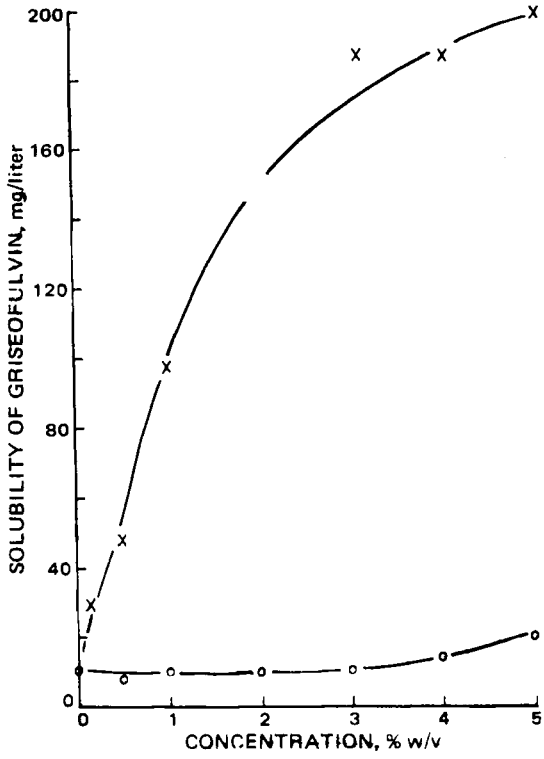

Figure 1—*Solubility of griseofulvin in aqueous solutions of II (×) or I (○) at 37°.*

Surface Tension Measurements—The Du Noüy tensiometer[7] (13) was used, and triplicate readings were taken.

Viscosity Measurements—Viscosity measurements were taken on aqueous solutions of I and II using a cone and plate rheometer[8].

Particle-Size Analysis—The particle-size analysis was carried out using an electronic particle counter[9] with 0.9% (w/v) aqueous NaCl[10], previously saturated with the drug, as the electrolyte.

Optical Microscopy—The drug particles released from dispersion systems were suspended in water saturated with the drug in question. A drop of the suspension on a microscope slide was examined and photographed using a light microscope with a camera attachment.

RESULTS

Effects of Excipients on Aqueous Solubility of Drugs and on Surface Tension and Viscosity of Water—Compounds I and II were reported by the manufacturers to be miscible with water in all proportions. This claim was confirmed for the samples purchased.

Figures 1 and 2 show that the presence of dissolved I or II increased the solubility of griseofulvin or tolbutamide in water. However, a given concentration of II brought about a much greater increase in the solubility of each drug than did the same concentration of I. For example, griseofulvin and tolbutamide were more soluble in 0.5% (w/v) II than in the same concentration of I by factors of about four and two, respectively; at the 5% (w/v) level, the factors were even greater (about 12 and five).

The presence of I or II lowered the surface tension of water (Fig. 3), and the effect was much greater for II. The sharp discontinuity in the curve for II occurs at the critical micelle concentration (CMC) (0.014% w/v). The absence of a discontinuity for I agrees with the fact that it is not a surface-active material and is unlikely to form micelles.

[1] Myrj 52, Atlas Chemicals Ltd., Carshalton, Surrey, England.
[2] Hoechst UK Ltd., Milton Keynes, Bucks, England.
[3] Specac, England.
[4] Fisons Ltd., Loughborough, England.
[5] Millipore (UK) Ltd., London, England.
[6] Cecil, Cambridge, England, or Beckman model 25, Glenrothes, Scotland
[7] Cambridge Instrument Co., Cambridge, England.
[8] Deer rheometer, Integrated Petronics Systems Ltd., London, England.
[9] Model TA/1, Coulter Electronics, Harpenden, England.
[10] Travenol, Thetford, Cambridgeshire, England.

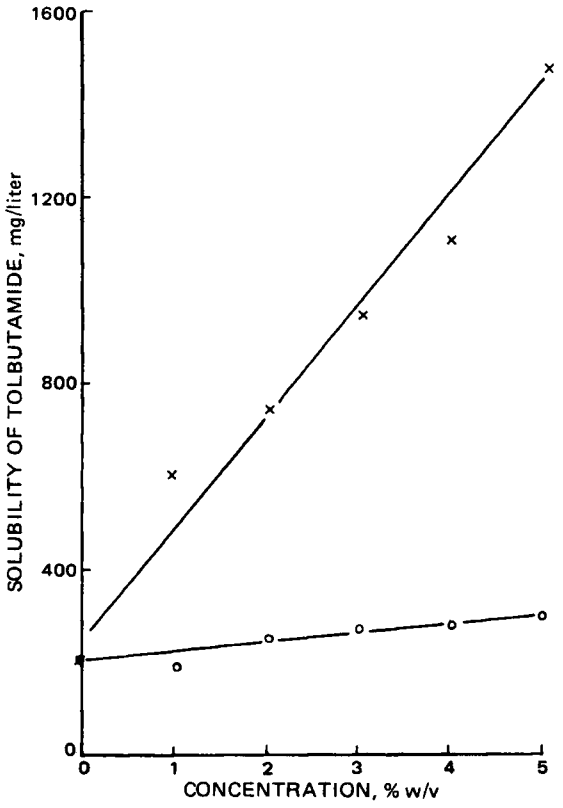

Figure 2—*Solubility of tolbutamide in aqueous solutions of II (×) or I (○) at 37°.*

From the negative gradients of the lines in Fig. 3, the surface excesses of the excipients were calculated by means of the Gibbs absorption isotherm and were found to be 0.178 and 1.09 moles/m^2 for I and II, respectively. From these values, the apparent area per molecule of excipient at the air–water interface was calculated to be 9.32 nm^2 for I and 1.53 nm^2 for II.

The viscosity of water (69 cps at 37°) was increased by the presence of II or I. At 37°, the viscosities were: 1% II, 70 cps; 10% (w/v) II, 103 cps; 1% I, 78 cps; and 10% (w/v) I, 98 cps. The viscosity was an approximately linear function of concentration within the 1–10% (w/v) range.

Dissolution Profiles of Nondisintegrating Disks of Pure Griseofulvin and Tolbutamide—The rate and extent of dissolution of nondisintegrating disks of griseofulvin (Fig. 4) and tolbutamide (Fig. 5) in water were reduced by increasing concentrations of I in the dissolution medium but were increased by increasing concentrations of II.

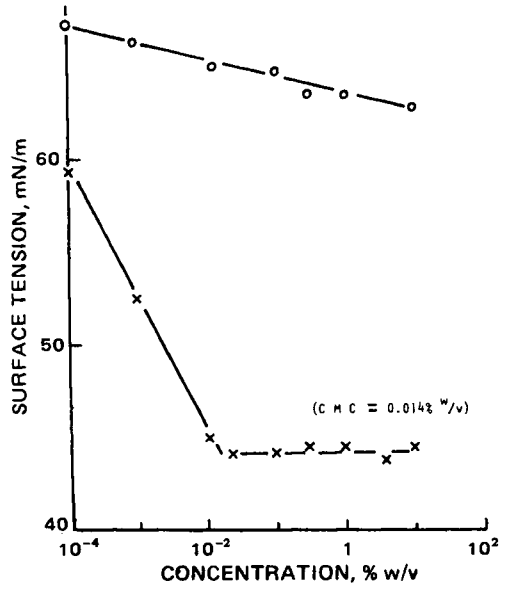

Figure 3—*Effect of concentration (log scale) of I (○) and II (×) on the surface tension of water at 37°.*

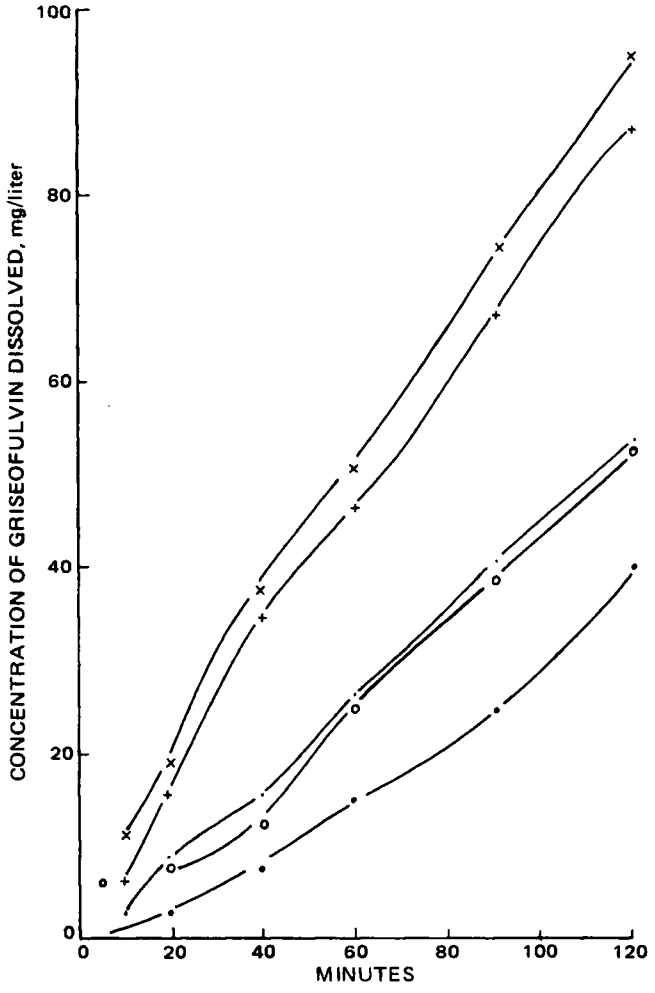

Figure 4—*Dissolution profile of nondisintegrating disks of griseofulvin in water (·), aqueous I at 0.1% (w/v) (○) and 1.0% (w/v) (●), and aqueous II at 0.1% (w/v) (+) and 1.0% (w/v) (×).*

Dissolution Profiles of Fused Dispersion Systems—Since just molten II dissolved up to 20% (w/w) tolbutamide (4), fused mixtures containing 10% (w/w) tolbutamide were selected for the preparation of compacts for dissolution in water and in pH 1 and 7 buffers. The negligible solubility of griseofulvin in just molten II (4) suggested that less of this drug would be more comparable with the tolbutamide preparations, so the fused griseofulvin mixtures chosen contained 2% (w/w) griseofulvin.

The compacted preparations disintegrated gradually by progressive erosion of the exposed surface, and the compacts of both drugs had disintegrated completely within 30 min. The concentration of drug released plateaued (Table I) after 60–120 min at values close to those corresponding to 100% release (10 mg/liter for griseofulvin and 50 mg/liter for tolbutamide). Microscopic examination of the solutions showed the absence of drug particles. The amount of drug in the 1-g compacts (100 mg of tolbutamide or 20 mg of griseofulvin) was insufficient to saturate the dissolution medium (2 liters).

Table I shows that the initial dissolution rate of griseofulvin (2% w/w) from fused dispersions in II was similar to that from fused dispersions in I, but the initial dissolution rate of tolbutamide (10% w/w) was ~45% greater from fused dispersions in II than from those in I. Thus, the dissolution of tolbutamide from fused dispersions was favored by II.

When 1 g of a fused mixture of griseofulvin or tolbutamide with I or II was added to 100 ml of water, a cloudy or frothy suspension was rapidly produced. On standing for a few hours, it gave a clear supernate and a fine powder at the bottom of the flask. By microscopic examination, it could be seen that, as a eutectic mixture was exposed to water, the excipient dissolved in water and a microcrystalline dispersion of the drug in water was obtained. After standing, some microcrystals grew to large macrocrystals at the expense of the smaller crystals. However, if 1 g was exposed

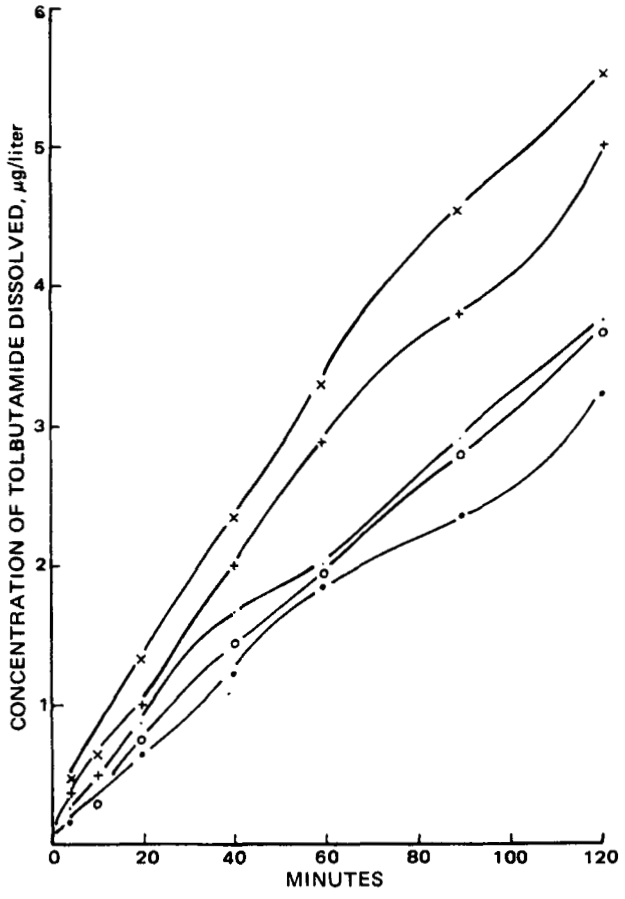

Figure 5—*Dissolution profile of nondisintegrating disks of tolbutamide in water (·), aqueous I at 0.1% (w/v) (○) and 0.5% (w/v) (●), and aqueous II at 0.1% (w/v) (+) and 0.5% (w/v) (×).*

to 1 liter or more of water, then no microcrystals or crystals were observed, because there was sufficient solvent to dissolve all of the drug from the eutectic mixture.

Dissolution Profiles of Coprecipitated Dispersion Systems—The composition of coprecipitated mixtures chosen for the dissolution rate analysis was 60% (w/w) griseofulvin or tolbutamide. Thus, 1 g contained 600 mg of either drug. This composition was a compromise between the need for an appreciable dilution of the solid drug and the need for an acceptable tablet or capsule weight in an eventual pharmaceutical preparation.

Microscopic examination of the coprecipitated mixtures showed agglomerates of micro- and macrocrystals of drug interspersed with the excipient.

In contact with the aqueous dissolution medium, the compacts disintegrated by progressive erosion of the exposed surface. Small floccules of drug crystals were obtained, not a uniform microcrystalline dispersion of the drug. The compacted preparation of each drug disintegrated completely, leaving no drug particles.

For a given dissolution medium, the amount of each drug released at any given time from a II coprecipitate was greater than that from the corresponding I coprecipitate (Figs. 6 and 7). The concentration of griseofulvin released in neutral dissolution medium reached a plateau after 60 min from II coprecipitates (Fig. 6). The plateau effect was not observed with the tolbutamide coprecipitates; this drug continued to be released after 120 min (Fig. 7). The amount of drug incorporated into the 1-g compacts (600 mg of tolbutamide or griseofulvin) was in excess of the amount required to saturate 2 liters of water (the volume of the dissolu-

Table I—Initial Dissolution Rate and Final Mean Concentration Attained between 60 and 120 min after Introducing Fused Dispersions (1 g) Containing Griseofulvin or Tolbutamide in Polyethylene Glycol 2000 (I) or Polyoxyethylene 40 Stearate (II) into Aqueous Solution (2 Liters)

Fused Dispersion System	Initial Dissolution Rate, mg/liter/min			Final Mean Concentration, mg/liter		
	pH 1	Water	pH 7	pH 1	Water	pH 7
2% (w/w) Griseofulvin + I	0.62	—	0.52	10.2	—	10.1
2% (w/w) Griseofulvin + II	0.53	0.57	0.54	8.1	8.8	8.9
10% (w/w) Tolbutamide + I	2.66	—	2.83	60.4	—	49.6
10% (w/w) Tolbutamide + II	3.96	3.99	4.02	55.7	52.0	51.5

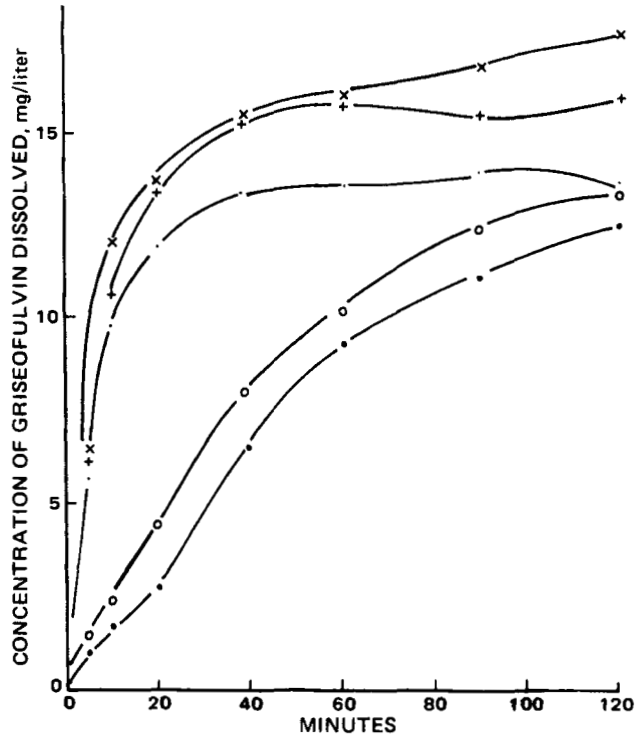

Figure 6—*Dissolution profiles of coprecipitated dispersions of griseofulvin (60% w/w) with I in pH 1 buffer (○) and pH 7 buffer (●) and of griseofulvin (60% w/w) with II in water (·), pH 1 buffer (×), and pH 7 buffer (+).*

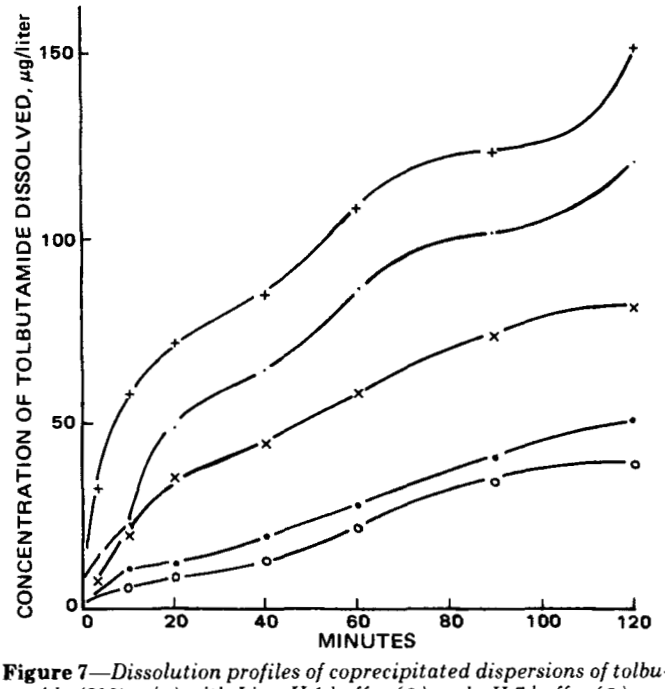

Figure 7—*Dissolution profiles of coprecipitated dispersions of tolbutamide (60% w/w) with I in pH 1 buffer (○) and pH 7 buffer (●) and of tolbutamide (60% w/w) with II in water (·), pH 1 buffer (×), and pH 7 buffer (+).*

Table II—Initial Dissolution Rate and Final Mean Concentration Attained between 60 and 120 min after Introducing Coprecipitated Dispersions (1 g) Containing Griseofulvin in Polyoxyethylene 40 Stearate (II) into Aqueous Solution (2 Liters)

Coprecipitated Dispersion	Initial Dissolution Rate, mg/liter/min		Final Mean Concentration, mg/liter	
	pH 1	pH 7	pH 1	pH 7
12.5% (w/w) Griseofulvin in II	0.507	0.322	18.2	14.9
60% (w/w) Griseofulvin in II	1.22	0.980	16.9	12.9

tion medium). Therefore, the II that was dissolved from the compact was solubilizing each drug.

To test the effect of the griseofulvin concentration, 1-g compacts of a coprecipitate containing 12.5% (w/w) of this drug in II were studied (Table II). The amount of drug (125 mg) corresponds to a dosage level currently administered to patients. The 12.5% (w/w) griseofulvin coprecipitates disintegrated completely within 20 min, and microcrystals of griseofulvin were found at the bottom of the beaker after 180 min of dissolution. The concentration of drug released between 60 and 120 min from coprecipitates containing 12.5% (w/w) griseofulvin was much the same (~15 mg/liter) as from those containing 60% (w/w) of the drug. However, the initial dissolution rate from the 12.5% coprecipitates was about one-third of that from the 60% coprecipitates. Thus, a fivefold reduction in the concentration of the drug in II coprecipitates reduced the initial dissolution rate only threefold.

Changes in Particle-Size Distribution of Drugs before Formulation and during Disintegration—Fused dispersion systems containing 2% (w/w) griseofulvin or 10% (w/w) tolbutamide in II disintegrated rapidly, releasing drug particles whose size distribution was analyzed within 25–30 min of exposure of the dispersion systems to water. Different cooling rates of the fused mixtures during preparation of the dispersion systems prior to compression might be expected to affect the particle-size distribution of the drugs. Comparison of the size distribution of griseofulvin particles released from the dispersion systems with that of the micronized drug originally supplied showed only relatively small differences, which bore no obvious relationship to the cooling rate. Thus, fused-cooled and coprecipitated dispersions released griseofulvin particles that were similar in appearance to those of the original (micronized) griseofulvin. These particles were difficult to discern under the microscope.

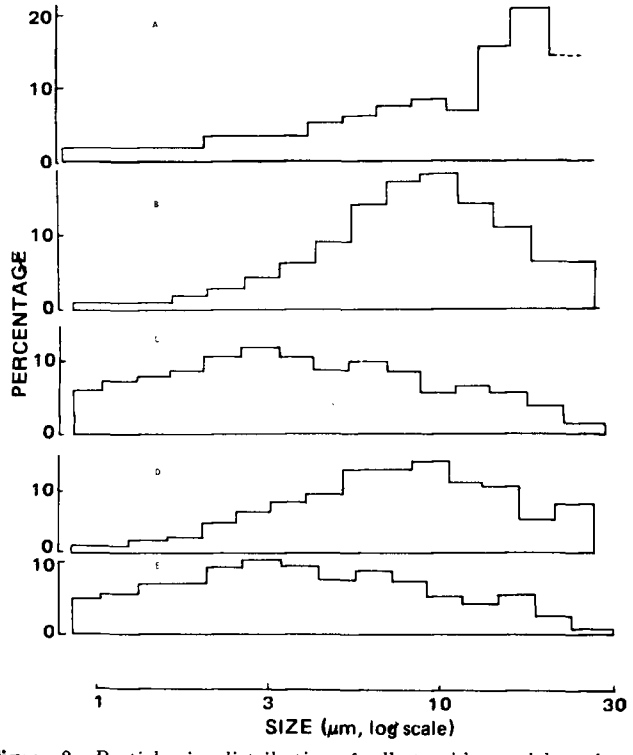

Figure 8—*Particle-size distribution of tolbutamide particles released (into electrolyte saturated with tolbutamide) from the original powder (A) and from fused mixtures of tolbutamide (10%) in II cooled slowly in a paraffin bath (B), cooled by natural cooling to 20° (C), cooled by refrigeration at 4° (D), and cooled rapidly in solid carbon dioxide to −78° (E).*

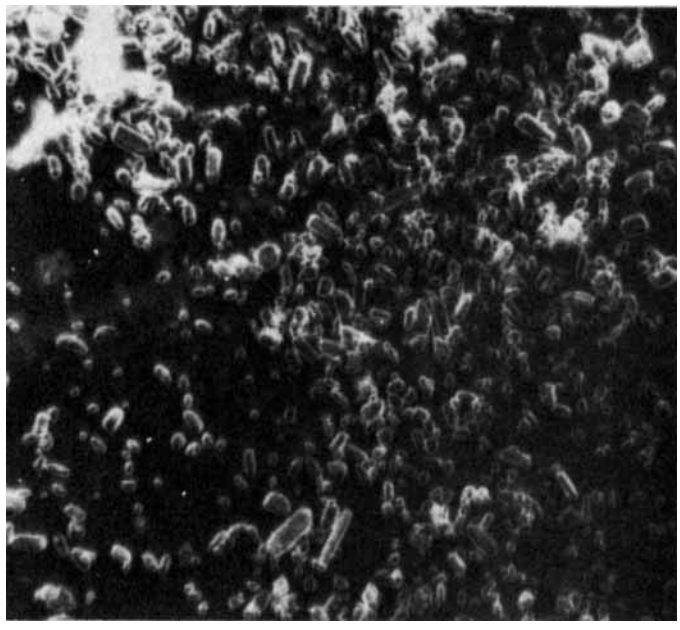

Figure 9—*Micrograph of tolbutamide particles released from a coprecipitated dispersion of tolbutamide (10% w/w) and II into aqueous sodium chloride solution (0.9% w/w) previously saturated with tolbutamide (×100).*

Although dispersion in II did not reduce significantly the particle size of micronized griseofulvin, it did reduce the particle size of commercial tolbutamide. Figures 8 and 9 show that the tolbutamide powder supplied consisted of particles with a mean diameter of ~20 μm or more, and the distribution suggests that some particles with a mean diameter of >30 μm were present, beyond the upper range of the particle counter. Figure 8 shows that the tolbutamide particles released from the fused and cooled dispersion systems in II were considerably smaller, with the mean particle diameters being 3–10 μm. There were relatively small differences between

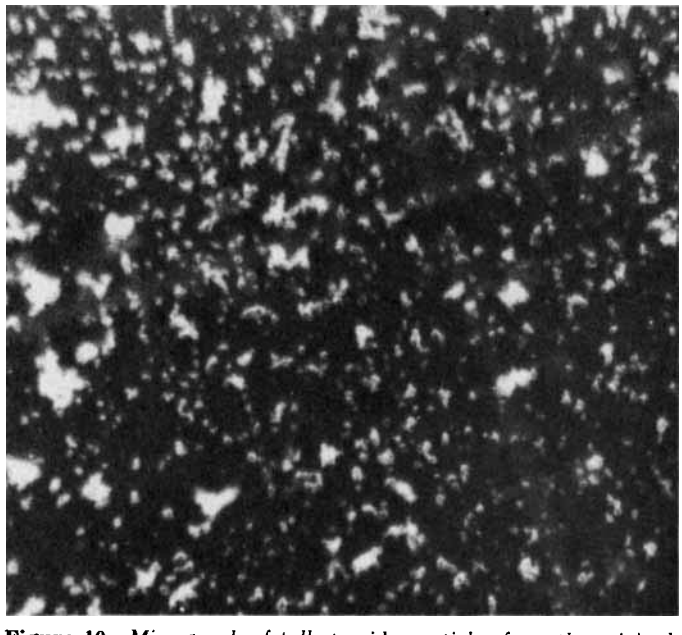

Figure 10—*Micrograph of tolbutamide particles from the original commercial sample of the drug from which the dispersion systems were prepared. The particles were suspended in aqueous sodium chloride solution (0.9% w/w) previously saturated with tolbutamide (×100).*

the size distribution elicited by different cooling rates, but no obvious relationships were apparent. The microscopic appearance of the small tolbutamide particles released from the fused–cooled dispersion systems in II was indistinguishable from that of tolbutamide released from coprecipitated dispersions in II (Fig. 10). The original tolbutamide particles clearly were much larger (Fig. 9).

DISCUSSION

The presence of I in water exerts little solubilizing action on griseofulvin (Fig. 1) or tolbutamide (Fig. 2). This finding agrees with a previous report (3) on the influence of longer polyoxyethylene molecules (polyethylene glycol 6000) on the solubility of griseofulvin. On the other hand, the presence of II in water considerably increases the solubility of both griseofulvin (Fig. 1) and tolbutamide (Fig. 2) by a process of micellar solubilization (Fig. 3) at II concentrations greater than 0.014% (w/v) (the critical micelle concentration). This finding agrees with the reported influence (14) of various nonionic surface-active agents, including some related polyoxyethylene derivatives, on the solubility of griseofulvin.

The presence of II in the aqueous dissolution medium also increases the dissolution rate of solid compressed disks of both drugs (Figs. 4 and 5). The experiments show that micellar solubilization, by increasing the drug solubility at the solid–liquid interface, plays a major role in increasing the dissolution rate of the drugs from solid dispersions of II. However, the presence of 0.1–1.0% (w/v) I in the aqueous dissolution medium actually reduces the dissolution rate of solid compressed disks of griseofulvin or tolbutamide (Figs. 4 and 5). This effect may result from the marked increase in viscosity of the aqueous dissolution medium, which is brought about by the presence of I. Since the diffusivity of small molecules frequently is inversely proportional to the solution viscosity, the effect of I suggests that dissolution of both griseofulvin and tolbutamide is diffusion controlled. The increase in viscosity then would reduce the diffusion rate of the drug in the diffusion layer and thereby reduce the dissolution rate. Evidently, the marked increase in viscosity (a 12% increase is produced by 1% I) more than compensates for the small increase in the solubility of each drug (increase of ~5% produced by 1% I).

Although the viscosity of water is increased by both II and I, the effect is greater for I at low concentrations since the viscosity of water is virtually unaffected by the presence of up to 1% II. Thus, solubilization and viscosity phenomena both favor II over I in promoting dissolution of the drugs, whereas viscosity increases actually disfavor solutions of I compared with pure solvent or buffer solutions (Figs. 4 and 5). This discussion readily explains the greater release rate of griseofulvin and tolbutamide from coprecipitates with II than from coprecipitates with I as the excipient (Figs. 6 and 7). The excipients dissolve rapidly due to their high solubility in water, and this dissolution creates the conditions in solution that influence the dissolution rate.

The difference between I and II as excipients for fused dispersion systems was less marked for griseofulvin than for tolbutamide. This result is apparent in the dissolution behavior of fused drug–excipient mixtures (Table I) and in the phase diagrams of the dispersion systems (4). The mean particle size of griseofulvin was changed little by incorporation into fused II dispersions and subsequent release by dissolution, but that of tolbutamide (Fig. 8) was reduced greatly. These differences may be accounted for by the low solubility of griseofulvin in each molten excipient and by the much greater solubility of tolbutamide in molten II than in molten I (4). On rapid cooling of a solution, the deposited solute, in this case solid tolbutamide, usually has a reduced particle size, because the rate of crystal nucleation is increased relative to the rate of crystal growth (15). When the dispersion systems are prepared by coprecipitation from ethanol, the differences in the dissolution rate between I and II as excipients are as large for griseofulvin as for tolbutamide (Figs. 6 and 7). In these cases, the particles of solid drug are deposited from solution in ethanol, and this process is largely independent of the precise nature of the excipient. Other factors, particularly solubility in and the viscosity of the dissolution medium, then can exert an overwhelming influence.

The release rate of tolbutamide from dispersion systems in polyethylene glycol 4000 or 6000 was found to be greater from coprecipitated dispersions than from fused dispersions (7). The state of subdivision, *i.e.*, the total surface area of the drug, seems the most likely explanation for differences arising from the method of preparation of the dispersion systems.

Polymorphic changes did not occur in the preparation of the dispersion systems (4) and, therefore, cannot be used to explain any of the phenomena reported here.

The surface activity of II may be advantageous in promoting the bioavailability of griseofulvin. For instance, II may be capable of acting like bile salts, which can solubilize and increase the dissolution rate of griseofulvin and other drugs (16–18). In this connection, polyoxyethylene 40 stearate, like the triglycerides, possesses a fatty acid residue, although the ability of triglycerides to increase the bioavailability of griseofulvin is claimed to be due solely to enhanced dissolution and not to enhanced absorption of the dissolved drug (19).

REFERENCES

(1) K. Sekiguchi and N. Obi, *Chem. Pharm. Bull.*, **9**, 866 (1961).

(2) W. L. Chiou and S. Riegelman, *J. Pharm. Sci.*, **60**, 1281 (1971).

(3) W. L. Chiou, *ibid.*, **66**, 989 (1977).

(4) R. Kaur, D. J. W. Grant, and T. Eaves, *ibid.*, **69**, 1317 (1980).

(5) N. N. Salib, S. A. El-Gamal, and A. A. Ismail, *Pharm. Ind.*, **38**, 918 (1976).

(6) "Toxicological Evaluation of Some Food Additives with a Review of General Principles and of Specifications," 17th report, FAO/WHO Expert Committee on Food Additives, FAO Nutrition Meetings Report Series 53, WHO Technical Report Series 539, Rome, Italy, 1974, p. 36.

(7) P. H. Elworthy and F. J. Lipscomb, *J. Pharm. Pharmacol.*, **20**, 817 (1968).

(8) T. R. Bates, S. L. Lin, and M. Gibaldi, *J. Pharm. Sci.*, **56**, 1492 (1967).

(9) W. L. Chiou, S.-J. Chen, and N. Athanikar, *ibid.*, **65**, 1702 (1976).

(10) R. Kaur, D. J. W. Grant, and T. Eaves, *J. Pharm. Pharmacol.*, **31S**, 48P (1979).

(11) "British Pharmacopoeia 1973," Her Majesty's Stationery Office, London, England, 1973, p. A-128.

(12) G. Levy and B. A. Hayes, *N. Engl. J. Med.*, **262**, 1053 (1960).

(13) W. D. Harkins and J. F. Jordan, *J. Am. Chem. Soc.*, **52**, 1751 (1930).

(14) A. A. Kassem and N. M. Mursi, *Bull. Fac. Pharm. Cairo Univ.*, **9**, 11 (1970).

(15) J. W. Mullin, "Crystallisation," Butterworth, London, England, 1972.

(16) T. R. Bates, M. Gibaldi, and J. L. Kanig, *J. Pharm. Sci.*, **55**, 191, 901 (1966).

(17) T. R. Bates, M. Gibaldi, and J. L. Kanig, *Nature*, **220**, 1331 (1966).

(18) S. A. Said, H. M. El-Fatatry, and A. Sh. Geneidi, *Aust. J. Pharm. Sci.*, **NS3**, 42 (1974).

(19) J. A. Grisafe and W. L. Hayton, *J. Pharm. Sci.*, **67**, 895 (1978).