(1953).
(8) A. B. Sen and S. K. Gupta, *ibid.*, **39**, 369 (1962).
(9) B. M. Gupta, S. K. Khan, and U. Agarwal, *J. Sci. Ind. Res.*, **21**, 189 (1962).
(10) M. Seth and N. M. Khanna, *Indian J. Chem.*, **14**, 536 (1976).
(11) M. L. Gujral, K. N. Sareen, and R. P. Kohli, *Indian J. Med. Res.*, **45**, 207 (1957).
(12) K. C. Joshi, V. K. Singh, D. S. Mehta, R. C. Sharma, and L. Gupta, *J. Pharm. Sci.*, **64**, 1428 (1975).
(13) H. C. Scarborough, U.S. pat. 3,073,826 (1963).
(14) B. Camillo and A. David, *J. Pharm. Pharmacol.*, **12**, 501 (1960).
(15) G. B. Jackman, V. Petrov, and O. Stephensen, *ibid.*, **12**, 529 (1960).
(16) S. S. Parmar, L. D. Joshi, K. Kishore, and R. Kumar, *Biochem. Pharmacol.*, **15**, 723 (1966).
(17) J. P. Barthwal, S. K. Tandon, V. K. Agarwal, K. S. Dixit, and S. S. Parmar, *J. Pharm. Sci.*, **62**, 613 (1973).
(18) H. Kawada, E. Yoshinaga, I. Chiyomaru, and H. Ito, Japanese pat. 7,748,178 (1977); through *Chem. Abstr.*, **88**, 132018p (1978).
(19) L. Nuesslein, E. A. Pieroch, and K. Roeder, U.S. pat. 4,061,645 (1977); through *Chem. Abstr.*, **88**, 62397k (1978).
(20) K. John (Velsicol Chemical Corp.), U.S. pat. 4,052,193 (1977); through *Chem. Abstr.*, **88**, 22929d (1978).
(21) A. K. Sen Gupta and H. K. Misra, *Indian J. Chem.* **17**, 185 (1979).
(22) *Ibid.*, **18**, 381 (1979).
(23) A. K. Sen Gupta and H. K. Misra, *Agr. Biol. Chem., Jpn.*, **44**, 1009 (1980).
(24) F. Gagiu and Al. Mavrodin, *Bull. Soc. Chim. Fr.*, **3**, 1010 (1967).
(25) Japanese pat. 20,944 (1966); through *Chem. Abstr.*, **66**, 46430f (1967).
(26) P. N. Bhargava and R. Lakhan, *Curr. Sci.*, **36**, 575 (1967).
(27) H. Culbertoson, J. C. Decius, and B. E. Christensen, *J. Am. Chem. Soc.*, **74**, 4834 (1952).
(28) R. S. Varma, S. A. Imam, and W. L. Nobles, *J. Pharm. Sci.*, **62**, 140 (1973).
(29) J. G. Horshfall, *Bot. Rev.*, **5**, 357 (1945).
(30) W. M. Diggle and J. G. Gage, *Biochem. J.*, **49**, 491 (1951).
(31) S. Hestrin, *J. Biol. Chem.*, **180**, 249 (1949).

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Comparison of Polyethylene Glycol and Polyoxyethylene Stearate as Excipients for Solid Dispersion Systems of Griseofulvin and Tolbutamide I: Phase Equilibria

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Abstract □ Phase equilibrium diagrams were constructed based on hot-stage microscopy and differential scanning calorimetry of solid dispersions of griseofulvin or tolbutamide in polyethylene glycol 2000 or polyoxyethylene 40 stearate. The solid dispersions were prepared by physical mixing, fusion, and coprecipitation from ethanol. The phase diagrams were largely independent of the method of preparation of the dispersion systems. The diagrams were of the monotectic type for polyethylene glycol 2000 with each drug and for griseofulvin with each excipient, with the monotectic species being the pure drug. Polyoxyethylene 40 stearate with tolbutamide gave eutectic systems in which liquid polyoxyethylene 40 stearate dissolved up to 20% of the tolbutamide. The phase diagrams showed greater solubility of tolbutamide in liquid polyoxyethylene 40 stearate than in polyethylene glycol 2000 but showed a similar solubility of griseofulvin in each excipient. Solid solution formation was not detected.

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

The use of a eutectic mixture containing a water-soluble compound to increase the dissolution rate and bioavailability of a sparingly soluble drug first was demonstrated by Sekiguchi and Obi (1). As the water-soluble matrix dissolves, the insoluble drug is exposed to the dissolution medium in a very fine state of subdivision. This type of formulation, a solid dispersion system, has been investigated extensively and has been extended to include solid solutions of drug in water-soluble excipients (2). Solid solutions should offer greater increases in the dissolution rate and bioavailability than eutectic mixtures, because the drug is dispersed as single molecules in solid solutions but as solid microscopic particles in the latter case.

BACKGROUND

Solid dispersions of griseofulvin in polyethylene glycols of high molecular weight (3, 4) have excited much interest. The dissolution rate and bioavailability of griseofulvin from such solid dispersions clearly are greater than those of the micronized or microcrystalline drug (5). These phenomena previously were attributed to the formation of solid solutions, but Chiou (6) recently showed that griseofulvin has negligible or very limited solid solubility in polyethylene glycol dispersion systems. The marked enhancement of the dissolution and absorption rates of griseo-

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Table I—Effect of Pretreatment on the Melting Ranges

Compound	Ground Materials	Recrystallized from Ethanol	After Fusion and Cooling
I	53–58°	53–58°	54–58°
II	46–50°	46–50°	37–45°
Griseofulvin	220–222°	220–222°	220–224°
Tolbutamide	127–133°	127–133°	125–131°

fulvin dispersed in polyethylene glycol seems to be primarily a result of the reduced size of the griseofulvin crystals; however, other factors, such as increased wettability, reduction or absence of aggregation and agglomeration, and solubilization of the drug by the carrier at the diffusion layer of particles also may contribute (6).

The formation of solid dispersions of tolbutamide in polyethylene glycol polymers also increases the dissolution rate of this drug (7), and this increase 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. Polyethylene glycol is a hydrophilic polymer with no hydrophobic or lipophilic moiety and, therefore, is not surface active. Esterification with a long-chain *n*-acyl residue (such as stearate, to form, for example, polyoxyethylene stearate) produces a water-soluble, surface-active macromolecule, which might offer certain advantages as an excipient in solid dispersion systems of drugs, such as griseofulvin or tolbutamide, that are poorly soluble in water. The nonpolar hydrophobic moiety, *e.g.*, $C_{17}H_{35}$, might promote solid solution formation, with consequent advantages for drug release, as well as surface activity, a potent factor in enhancing rates of dissolution and absorption. The possibility of solid solution formation is considered in the present report, and the consequences of surface activity are discussed elsewhere (8).

Polyoxyethylene 40 stearate has been evaluated by the joint Food and Agriculture Organization and World Health Organization Expert Committee on Food Additives (9) and is claimed to be acceptable for daily intake of up to 25 mg/kg. Further biological data, including biochemical aspects, toxicological studies, and observations in humans, also have confirmed the relative nontoxicity of polyoxyethylene 40 stearate (10–15).

Polyoxyethylene 40 stearate is a mixture of monoacid stearates of polyoxyethylene polymers consisting of 40 oxyethylene units on the average, and its mean molecular weight is similar to that of polyethylene glycol 2000. It is a solid that melts at 45–52° and is miscible with water in all proportions. Its hydrophile–lipophile balance value is 16.9, and it stabilizes oil-in-water emulsions.

Using thermal methods of analysis, the physicochemical interactions between two model drugs and polyoxyethylene 40 stearate (average molecular weight of 2044) were compared with those between the drugs and polyethylene glycol 2000. The model drugs, griseofulvin and tolbutamide, were chosen based on their low solubility in water and biological fluids.

Dispersion systems containing each drug and each excipient were prepared (*a*) by grinding the drug and excipient together, (*b*) by fusing the drug and excipient together and then grinding the mass, and (*c*) by coprecipitating the drug and excipient from the same solvent (ethanol) followed by grinding. Mixtures covering the entire range of composition, including the single components, were subjected to differential thermal analysis and hot-stage microscopy, from room temperature to temperatures above those of complete melting. The solid–liquid phase diagrams were plotted and compared.

The next report in this series (8) compares the influence of polyoxyethylene 40 stearate (II) with that of polyethylene glycol 2000 (I) on the dissolution rate of the two drugs from certain dispersion systems and assesses the factors responsible for the differences. A preliminary report of the work was published previously (16).

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 (17). The pH 1 buffer was 0.1 *M* HCl. All water was double distilled from an all-glass still.

[1] Myrj 52, Atlas Chemicals Ltd., Carshalton, Surrey, England.
[2] Hoechst UK Ltd., Milton Keynes, Bucks, England.

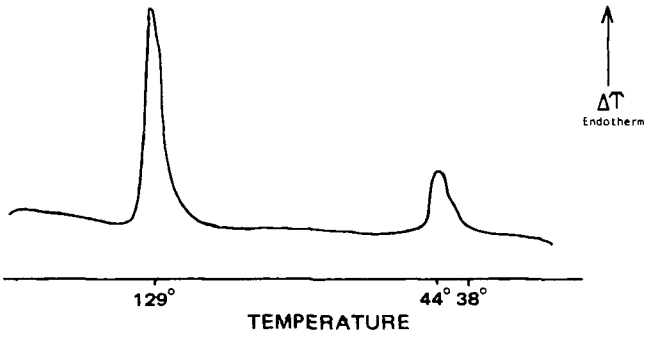

Figure 1—*Differential thermal analysis curve of a coprecipitated dispersion of tolbutamide (90% w/w) and II (10% w/w).*

Preparation of Dispersion Systems—*Physical Mixtures*—The physical mixtures were prepared by thoroughly grinding together weighed quantities of the drug and excipient for 5 min using a glass pestle and mortar. Homogeneity of the mixtures was tested by subjecting the samples to thermal microscopy and to differential thermal analysis.

Fused Mixtures—The fused mixtures were prepared by heating 1–2 g of the corresponding ground physical mixture in a wide test tube to a few degrees above the melting point of the excipient, *i.e.*, <65°, with rotation of the tube for 30 sec. The sample was allowed to cool in a desiccator at 4°. The resulting solid then was scraped out of the tube and ground using a glass pestle and mortar.

Coprecipitated Mixtures—Coprecipitated mixtures were prepared by dissolving weighed quantities of the drug and excipient in ethanol, mixing thoroughly, and allowing the solvent to evaporate slowly in a rotary film evaporator[3] at ~40° under vacuum. The resulting semisolid mass was dried under vacuum[4] at 20° in the presence of phosphorus pentoxide. The dry solid was ground using a glass pestle and mortar.

Differential Thermal Analysis—Five milligrams of sample was heated at 5°/min in a thermal analyzer[5] coupled to a two-channel potentiometric recorder[6]. Alumina was used as the reference material, and static air was the gas phase. The instrument was calibrated using benzoic acid[7] (thermochemical grade).

The onset of each peak was characterized by the temperature at the point of intersection of the line of the steepest slope and the baseline. The completion of each peak was characterized by the temperature at the summit. These two temperatures were used to define the melting ranges from differential thermal analysis.

Hot-Stage Microscopy—About 1 mg of sample was placed between a microscope slide and a cover slide and heated at 1–5°/min under a hot-stage microscope[8] fitted with polarizers. The onset of melting was characterized by the first appearance of liquid, and the completion of melting was considered as the final disappearance of solid. These two temperatures were used to define the melting ranges from hot-stage microscopy.

Preparation of Dispersion Systems for Differential Thermal Analysis and Hot-Stage Microscopy—The excipients under study are waxy at room temperature and crystalline and brittle at the temperature of solid carbon dioxide. Therefore, differential thermal analysis and hot-stage microscopy of the excipients were compared after grinding at each temperature followed by standing for 30 min in a desiccator. Since no significant difference in melting was found, grinding subsequently was carried out at room temperature.

Using differential thermal analysis and hot-stage microscopy, the phase equilibria of physical, fused, and coprecipitated mixtures of each drug (tolbutamide and griseofulvin) with each excipient (I and II) were studied.

RESULTS

Melting Behavior of Original Materials—Compounds I and II, griseofulvin, and tolbutamide, when subjected to differential thermal analysis, each gave a single peak corresponding to fusion. Furthermore,

[3] Buchi, Switzerland.
[4] Vacuum drier, Gallenkamp, London, England.
[5] Stanton Redcroft model 671, London, England.
[6] Servoscribe 2S, Smiths Industries Ltd., Cricklewood, London, England.
[7] BDH Chemicals Ltd., Poole, Dorset, England.
[8] Kofler type, C. Reichert Optische Werke, Austria.

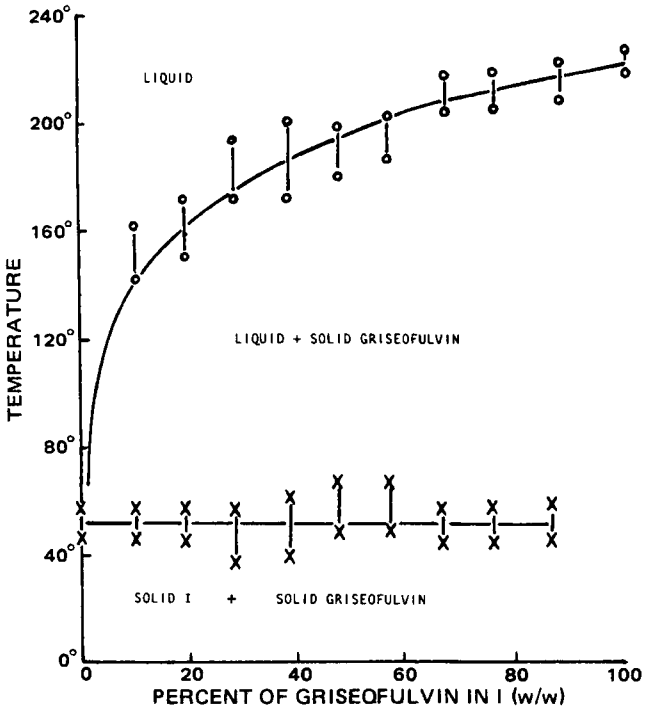

Figure 2—*Phase diagram of coprecipitated mixtures of griseofulvin and I determined using differential thermal analysis and hot-stage microscopy.*

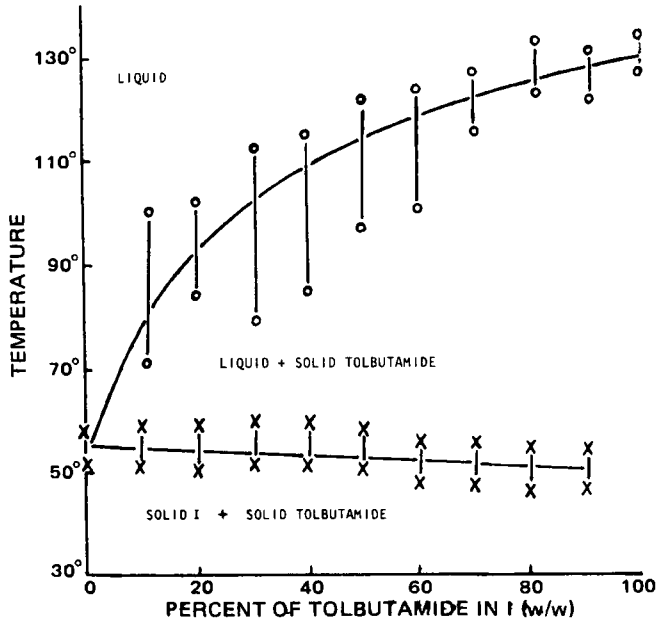

Figure 4—*Phase diagram of coprecipitated mixtures of tolbutamide and I determined using differential thermal analysis and hot-stage microscopy.*

when heated slowly under hot-stage microscopy, each substance melted over the same temperature range as that defined by the beginning and summit of the corresponding peak in differential thermal analysis. The two techniques afforded the melting ranges shown in Table I. Reductions in the melting point were observed only with tolbutamide and II after fusion and cooling.

Melting Behavior of Drug–Excipient Mixtures—Whether prepared by physical mixing, fusion–cooling, or coprecipitation, dispersion systems of each drug (griseofulvin or tolbutamide) in each excipient (I or II), exhibited two transitions in differential thermal analysis (Fig. 1). These transitions corresponded to fusion of the excipient and drug, respectively, as observed under hot-stage microscopy over the temperature range studied. The lower temperature transition always corresponded to fusion of I or II, and the higher temperature transition always corresponded to fusion of griseofulvin or tolbutamide. This behavior and the corresponding binary phase diagram were qualitatively independent and quantitatively almost independent of the method used to prepare a given drug–excipient mixture. Typical phase equilibrium diagrams are shown in Figs. 2–5.

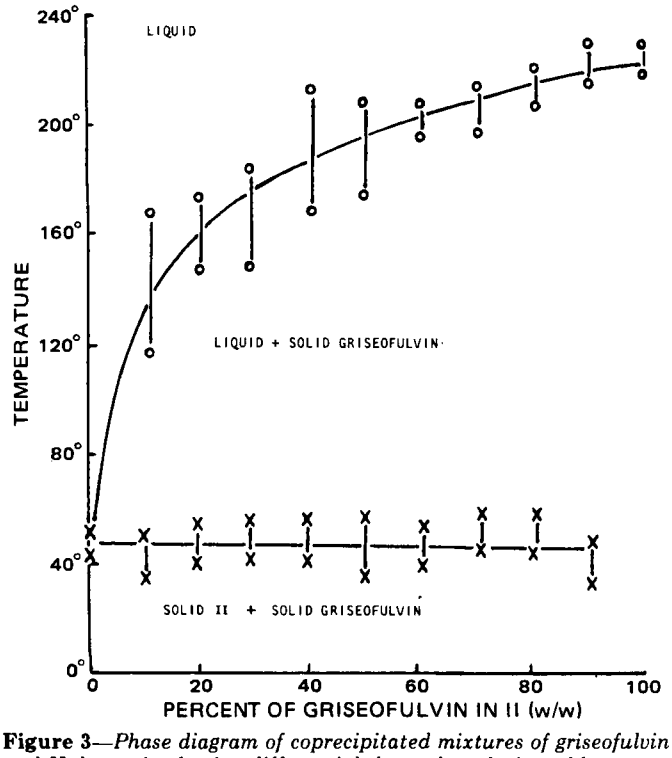

Figure 3—*Phase diagram of coprecipitated mixtures of griseofulvin and II determined using differential thermal analysis and hot-stage microscopy.*

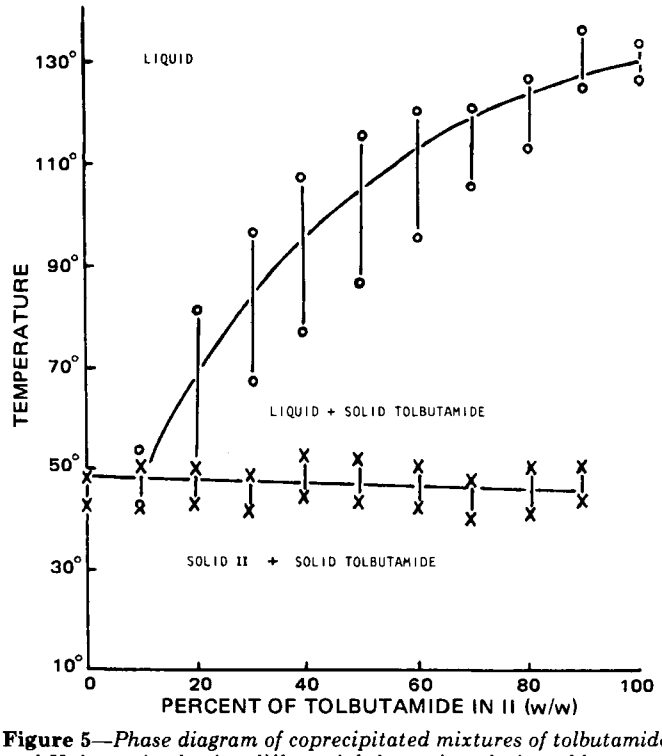

Figure 5—*Phase diagram of coprecipitated mixtures of tolbutamide and II determined using differential thermal analysis and hot-stage microscopy.*

Table II—Classification of Phase Equilibrium Diagrams

Drug	Excipient I			Excipient II		
	Physical Mixing	Fusion	Coprecipitation	Physical Mixing	Fusion	Coprecipitation
Griseofulvin	A	A	A	A	A	A
Tolbutamide	A	A	A	B	B	B

Hot-stage microscopy of the mixtures of all compositions showed a constant melting point of I at 48–58° and of II at 42–52°, corresponding to the endothermic peaks in differential thermal analysis (the solidus or melting point). Hot-stage microscopy showed that, in general, increasing amounts of drug dissolved in the liquid excipient as the temperature increased so that the drug crystals disappeared completely at a temperature (the liquidus or freezing point) between the melting point of the excipient and the melting point of the pure drug. The freezing point was quoted as that temperature above which no more crystals were visible between crossed polarizers. If this transition was not sharp, the sample was allowed to cool gradually and the freezing point was recorded as that temperature at which drug crystals just became visible. Crystals of griseofulvin and tolbutamide have distinctive crystalline habits, which are clearly recognizable compared with the amorphous appearance of the excipients. As the drug crystals dissolved in the liquid excipient on heating, their corners and edges were eroded first, as is normally encountered (18).

When the proportion of each drug in each solid dispersion system was increased, hot-stage microscopy and differential thermal analysis showed, in general, that the solidus temperature (freezing point of the drug) increased. This solidus transition appeared as a second endothermic peak in differential thermal analysis, but the instrument, unlike hot-stage microscopy, was unable to detect this transition for a drug content of <~50% (w/w). Thus, in general, the two techniques were confirmatory or complementary, and no evidence of polymorphism was apparent from either method.

Each of the 12 phase diagrams (2 drugs × 2 excipients × 3 methods of mixing) fell into one of two groups, arbitrarily designated as Types A and B (Table II). Type A was a monotectic system and occurred with all six griseofulvin systems and with the three tolbutamide–I systems. It was characterized by the absence of complete dissolution of the drug in the molten excipient at the melting point of the excipient. Examples of a Type A phase equilibrium diagram are shown in Figs. 2–4. There was very limited solubility of solid griseofulvin in just molten I (Fig. 2) or just molten II (Fig. 3).

Type B diagrams were shown by the three tolbutamide–II systems and were characterized by features common to both eutectic and monotectic behavior. Figure 5 gives an example for the coprecipitated tolbutamide–II system. The liquid II at its melting point (~50°) was capable of dissolving ~10% (w/w) tolbutamide. This contrasts sharply with the immeasurably low solubility of the drug in liquid I at its melting point (Fig. 4).

For any one of the four drug–excipient pairs, the methods of preparing the dispersion systems gave almost identical diagrams with the following exceptions:

1. Physical and fused mixtures of tolbutamide and II gave approximately twice the solubility of tolbutamide in just molten II, as did the coprecipitated mixtures; *i.e.*, concentrations of ~20% were obtained.

2. Physical mixtures of griseofulvin and I showed a more steeply rising liquidus curve than did the fused or coprecipitated systems.

Liquid mixtures containing 1% (w/w) griseofulvin or tolbutamide in I or II froze to a solid, which microscopic examination showed to consist of drug crystals dispersed in the excipient. Therefore, the extent of solid solubility of each drug in each excipient was judged to be negligible (<1% w/w).

DISCUSSION

The only form of tolbutamide encountered under the conditions of the present work was the commercial form which melted at 127° (19), namely, Modification A (20) or I (21, 22). This polymorph is the most stable at room temperature (21, 22). In view of the reported polymorphism of tolbutamide (19–22), it may seem surprising that no polymorphic transitions were observed in the present work; this finding is illustrated by the differential thermal analysis plot shown in Fig. 1. The most likely explanation is that either polymeric polar excipient (polyethylene glycol 2000 or polyoxyethylene 40 stearate) stabilizes the original commercial modification (I or A) relative to the other modifications produced under different conditions (19–22). In an analogous manner, the presence of the polar polymer povidone, for example, slows down the rate of transformation of the polymorphic form (II) of sulfameter to form III in aqueous suspension (23).

All of the phase diagrams involving I or griseofulvin, either separately or together, were of the monotectic type (Figs. 2–4). This type of system has not been reported previously in pharmacy but is well known to metallurgists, *e.g.*, the silicon–tin system (24).

A monotectic phase diagram has the form of a eutectic diagram in which one arm is missing and in which the lower melting component replaces the eutectic composition. The rising liquidus curve on the left of each monotectic diagram corresponds to the solubility curve of the drug in the liquid excipient.

Comparison of the phase diagrams (Figs. 2–5) shows that the differences between I and II as excipients for solid dispersion systems are much less marked for griseofulvin than for tolbutamide dispersions. The position and shape of the rising curve at the left of each phase diagram show a greater solubility of tolbutamide in liquid II than in I (Figs. 4 and 5) but a similar solubility of griseofulvin in each (Figs. 2 and 3).

The phase diagrams for the tolbutamide–II dispersions prepared in three ways can be considered to be eutectic systems in which the liquidus (freezing-point curve of tolbutamide) and the solidus (melting-point curve of II) have become superimposed. The first molten II (at ~40°) is capable of dissolving completely up to 10 or 20% (w/w) tolbutamide, depending on the preparation method.

However, the phase diagrams of the dispersion systems are changed little by the preparation method and appear to be dominated by the solvent properties of liquid I or II for each drug. The presence of a small amount of I or II with each drug causes little depression of the melting point of the drug, and, conversely, the presence of a small amount of griseofulvin or tolbutamide hardly affects the melting point of the excipient. This behavior contrasts sharply with the dispersion systems using small molecules as excipients, *e.g.*, urea (25, 26), succinic acid (27), and citric acid (28). These systems are eutectic with or without the formation of solid solutions. All of the dispersion systems of griseofulvin or tolbutamide with I or II showed negligible formation of solid solutions (<1% w/w), in contrast to the small molecule systems. This absence of solid solutions in polyethylene glycol–griseofulvin systems also was reported on the basis of X-ray diffraction evidence (6).

Finally, the phase diagrams obtained for fused–cooled and coprecipitated mixtures of each drug with each excipient were similar to those of physical mixtures of the two components, and there was no evidence of the formation of solid complexes between the two components. This absence of chemical interactions between the drug–excipient pairs on fusion, which was reported earlier for polyethylene glycol with griseofulvin (3) and tolbutamide (29), indicates that I or II can only influence the dissolution rate of the drugs by altering their surface properties such as the surface area or the nature of the drug–water interface. These factors were considered in a separate report (8).

REFERENCES

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

(2) A. H. Goldberg, M. Gibaldi, J. L. Kanig, and M. Mayersohn, *J. Pharm. Sci.*, **55**, 581 (1966).

(3) W. L. Chiou and S. Riegelman, *ibid.*, **58**, 1505 (1969).

(4) W. L. Chiou and L. D. Smith, *ibid.*, **60**, 125 (1971).

(5) W. L. Chiou and S. Riegelman, *ibid.*, **60**, 1281 (1971).

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

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

(8) R. Kaur, D. J. W. Grant, and T. Eaves, *J. Pharm. Sci.*, **69**, 1321 (1980).

(9) "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.

(10) P. J. Culver, C. S. Wilcox, C. M. Jones, and R. S. Rose, Jr., *J. Pharmacol. Exp. Ther.*, **103**, 377 (1951).

(11) B. L. Oser and M. Oser, *Int. J. Nutr.*, **60**, 367, 489 (1956).

(12) *Ibid.*, **61**, 149, 235 (1957).

(13) O. G. Fitzhugh, A. R. Bourke, A. A. Nelson, and J. P. Crawley, *Toxicol. Appl. Pharmacol.*, **1**, 315 (1959).

(14) J. F. Treon, *Am. Perfum. Cosmet.*, **77**, 35 (1962).

(15) "Guide to the Physiological Suitability of Atlas Surfactants," ICI Americas, Wilmington, Del., 1977, pp. 8–11.

(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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