Preparation and Dissolution Characteristics of Several Fast-Release Solid Dispersions of Griseofulvin

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Abstract ☐ A marked increase of dissolution rates and attainments of supersaturation of griseofulvin were found when dispersed in the matrices of polyethylene glycol (PEG) 4000, 6000, 20,000, pentaerythritol, pentaerythrityl tetraacetate, and citric acid by the fusion or solvent methods. The exact physical nature of these dispersion systems are not determined. It is believed, however, that some griseofulvin is molecularly and/or colloidally dispersed in the PEG polymers due to their highly viscous and supercooling effect which will retard the nucleation and growth of griseofulvin precipitation during the solidification process. Pentaerythritol and pentaerythrityl tetraacetate which are globular compounds with the high degree of deformation of crystal lattice allowed are believed to form limited or complete solid solutions with griseofulvin. The melt of griseofulvin-citric acid mixture is highly viscous. It required several days of standing at 37° in order to transform to a form (glassy) which could then be pulverized. The resultant glass solution is believed to represent a new class of physical modification of drugs exhibiting strikingly fast dissolution rate of griseofulvin.

Keyphrases ☐ Griseofulvin fast-release solid dispersions—preparation ☐ Dissolution characteristics—griseofulvin fast-release solid dispersions ☐ Stability—griseofulvin solid dispersions ☐ UV spectrophotometry—analysis ☐ IR spectrophotometry—analysis ☐ Fluorometry—analysis ☐ TLC—analysis

In 1961, Sekiguchi and Obi (1) first proposed the utilization of solid dispersions to increase the dissolution and oral absorption of poorly water-soluble drugs. They proposed the formation of a eutectic mixture of a poorly water-soluble drug with a physiologically inert, easily soluble carrier. The physical mixture of the drug and the carrier was melted together and solidified by cooling to room temperature. When such systems are exposed to water or gastrointestinal fluids, the soluble carrier will dissolve rapidly and the finely dispersed drug particles will then be released. This is based on the assumption that solute particles formed from the solidification of the eutectic melt are usually very fine, almost in the micron or submicron range. Goldberg *et al.* (2) in 1965 suggested the formation of solid solution to reduce the particle size to a minimum, *i.e.*, insoluble drugs dispersed molecularly in the matrix of soluble, inert carriers. This can increase not only the dissolution rate, but also the solubility of drugs.

Griseofulvin (gris), a water-insoluble, antifungal antibiotic, has been shown to be incompletely and erratically absorbed after oral administration of the conventional or micronized gris to rats, rabbits, cats, and man (3–9). The slow dissolution rate in the gastrointestinal tract is the dominating factor in producing incomplete and irregular absorption. The rate of dissolution of gris *in vitro* was shown previously to be enhanced considerably when dispersed in succinic acid (10) or polyvinylpyrrolidone (11). However, neither of these systems has been tested for its efficacy and application in animals or humans.

This communication will report the usage of the higher molecular weight polyethylene glycols (PEG's), pentaerythritol, pentaerythrityl tetraacetate, and citric acid as water-soluble carriers in forming solid matrices for gris. In addition to the eutectic mixture and solid solution, a new class, glass solution (12), will be introduced. This is believed to be able to serve the same purpose of fast release of drugs as suggested for the solid solution. The *in vivo* evaluation of the dispersed gris in dog and in man will be reported in the future.

EXPERIMENTAL

Materials—Gris USP (micronized, Lot No. 0524),[1] polyethylene glycol 4000, 6000, and 20,000 (20 M);[2] pentaerythritol, reagent grade,[3] pentaerythrityl tetraacetate, reagent grade;[3] anhydrous citric acid, reagent grade;[3] succinic acid, reagent grade.[4]

METHODS OF PREPARATION OF SOLID DISPERSION

Direct Melting Method—Fine powders of gris and different water-soluble carriers such as polyethylene glycol (PEG) 400, 6000, and 20,000, pentaerythritol, pentaerythrityl tetraacetate, citric acid, and succinic acid were accurately weighed in certain ratios. They were physically mixed and transferred to beakers of a suitable size. These physical mixtures were heated directly and quickly with constant stirring on the conventional hot plate or oil bath until they all melted. The melts were quickly solidified by pouring onto stainless steel plates. In systems of gris-PEG, solidification was further facilitated by blowing cold air onto the opposite side of the plates. At ambient temperatures, the freshly prepared gris-citric acid mass was essentially transparent, but was viscous and not easily subdivided. On experimentation it was noted that the gris-citric acid mixture stored in an oven at 37° took several days to convert to a form which could be easily pulverized. Storage at or below room temperature retarded the conversion. The Gris-PEG mixtures also required storage in a desiccator to harden. The final solid masses were pulverized either in a mortar or by use of a small ball mill. The powders were sieve-sized to the 80 or 200 mesh range.

Solvent Method—Mixtures containing 10 and 20% (w/w) gris in the gris-PEG 6000 system were also prepared by the solvent method. In the 10% gris mixture, 0.5 g. of Gris and 4.5 g. of PEG 6000 were suspended in 500 ml. of absolute alcohol in a beaker and concentrated directly on a hot plate to about 100 ml. The resulting cloudy and colloid-like suspension was further concentrated in an oil bath kept at 115° for 1 hr., when the formation of ethanol vapor bubbles were no longer observed. A semitransparent, colloidal, viscous liquid was obtained which was allowed to solidify by cooling in a cold air stream. The sample was powdered and the 80 to 200 mesh fraction was collected. In the 20% Gris mixture, 0.5 g. of Gris and 2.0 g. of PEG 6000 were treated in the same manner except the sample was finally heated in an oil bath at 125° for 25 min. It was noted that the control of temperature and the time of heating affected the amount and the particle size of crystallization of gris.

Stability Studies on the Gris-Solid Dispersions—Thermal, spectroscopic, and chromatographic methods have been used to study the pure components and the components of the final dis-

[1] McNeil Laboratories, Fort Washington, Pa.
[2] Carbowax, Union Carbide Chemicals Co., S. Charleston, W. Va.
[3] Eastman Organic Chemicals, Rochester, N. Y.
[4] J. T. Baker Chemical Co., Phillipsburg, N. J.

persions to attempt to verify their chemical stability after processing.

Thermal Studies—The melting point of gris is 218–219°. The pure powder was melted quickly to 235° and the melting point of the rapidly solidified mass was measured by the capillary method to ascertain the effect of the heating process.

Spectrophotometric Studies—UV, IR, and fluorescent methods were used. The UV spectra of pure Gris and PEG 6000, heat-treated gris (235°) and PEG 6000 (300°), and Gris from different solid dispersions were run in 1% alcohol solution by the recording Beckman DB spectrophotometer. The activation and fluorescence spectra of the pure and processed Gris were run by using Aminco Bowman spectrophotofluorometer. The IR spectra of the pure and heat-treated gris were obtained from Beckman IR 8 spectrophotometer by the KBr disk method.

Thin-Layer Chromatography—The pure and processed gris samples were dissolved in absolute ethanol and spotted on the plates. The plates were developed by a solvent system of chloroform–acetic acid–water (4:1:1 v/v) and the phosphor was excited by 253 mμ light in darkness. The dark spots can be easily detected on the green background of the plates since gris and the possible decomposition products would absorb the light preventing fluorescence.

Dissolution Rate Studies—A recycling and automatic recording system was used for all the dissolution rate studies. The dissolution rates of gris in different physical forms were run in either 500 ml. distilled water in a 600-ml. beaker at room temperature or 18 l. of distilled water at 36.7 ± 0.05° in a constant temperature water bath.

Unless otherwise specified, samples of 80 to 200 mesh powder were transferred directly into the dissolution medium and stirred with a stainless steel paddle. The paddle, 5.5 × 2.7 cm., was placed at the center of 500 ml. dissolution medium and rotated at a rate of 100 r.p.m. A larger size paddle, 8.7 × 2.7 cm., was used for 18 l. of dissolution assembly. The paddle was placed 4 cm. above the bottom of the water bath and rotated at a rate of 200 r.p.m. The solution was pumped by a peristatic pump (Multi-speed Transmission, model No. 6000–000, available from the Harvard Apparatus Co., Dover, Mass.) at a rate of 80 to 100 ml./min. through a glass filter stick to a 1-cm. flow cell and then back to the dissolution apparatus. The absorbance of the solution is monitored by a recording Beckman DB spectrophotometer at either the maximum peak of gris, 292 mμ, or minimum absorbance, 272 mμ, depending upon the concentration of Gris. In the system of gris-PEG 20,000, 324 mμ was used because of possible interference of absorption by the polymer at 272 mμ. The volume of the solution in the tubing of the recycling system is about 10 ml. At the flow rate used, the monitored absorbance will reach 90% of the equilibrium value in 15 sec. Therefore the lag time in the measurement of dissolution rate is essentially negligible. In the study of the dissolution rate at room temperature, the water is preadjusted to 25°. The ambient temperature of the room ranged less than 2° from this temperature.

The solubility of gris at 25° is 1 mg./100 ml. of water. The amount of gris in the various solid dispersion systems used for the dissolution rate study in 500 ml. water was usually 5 mg., which would saturate this volume of the solvent (unless a polymorphic form of increased solubility was formed). Selected studies were carried out, however, using several times the amount of gris. Dissolution rate studies using 125 mg. gris were also carried out in 18 l. of water at 36.7°. The solubility of gris at 37° is 1.5 mg./100 ml. of water, hence 125 mg. of gris in 18 l. of water at that temperature is equivalent to about 46% of the saturation.

In order to study a gris sample of markedly different particle size, a mass of gris was rapidly melted, cooled, pulverized and sieved to a 100 to 200 mesh particle distribution. All samples were run in at least duplicate. The dissolution characteristics of the solid dispersions were reproducible with only negligible variation between runs. A slightly larger, but relatively insignificant variation was seen between runs of the coarse or micronized powder.

RESULTS AND DISCUSSION

Selection of Solid Dispersion Carriers—*Polyethylene Glycol Polymers*—Water-soluble polymers such as polyvinylpyrrolidone, methylcellulose, and polyvinylmethylether have been proposed as possible vehicles to form colloidal suspensions (13) or fast-release solid dispersions (11) of water-insoluble drugs by the solvent method. The authors have found a new class of water-soluble polymer, the polyethylene glycol polymer, not previously reported, which appears to be able to serve as an extremely useful solid dispersion matrix for water-insoluble drugs. One possible limitation of such systems may be the propensity of the ether group in the polyethylene glycol polymers to form stable and insoluble complexes with some drugs such as phenobarbital (14).

The rationale for the polyethylene glycol polymers as water-soluble carriers is based on the following theoretical considerations:

(*a*) Molecular size: the essential criterion for the formation of an interstitial solid solution is the molecular size, *i.e.*, the host molecule must be much larger than the guest (solute) molecule (15, 16), since the molecular weight of the organic drugs is usually below 400 or 500, while that of the available PEG is 1500, 4000, 6000, and 20,000. Therefore, the use of the high molecular weight polyethylene glycols will be expected to form interstitial solid solutions with many drugs.

(*b*) Supercooling and viscous effects: high molecular weight PEG compounds are viscous in their melted state even at a temperature of 200° (17) and can be supercooled to about 40° (the melting points of the different molecular weight of PEG's are all above 50°). The viscosity also increased markedly with the decrease in temperature. As the PEG-drug melt is allowed to cool, the crystallization of the drug will be retarded due to the slow migration and the difficulty in nucleation of the drug in the viscous medium (18, 19). Although the melting point of gris is 218–219° and that of the polymer is above 50°, it was found feasible to supercool 10, 20, and even 40% of gris in PEG 4000 or 6000 (w/w) to about 40° before solidification started. This surprising supercooling phenomenon of PEG-drug melt was also observed with other drugs such as digitoxin, 17-methyltestosterone, prednisolone acetate, and hydrocortisone acetate (20). It is believed that it will also occur with other substances.

As discussed above, the solidified PEG-drug melt is prepared by cooling rapidly on a cold stainless steel plate. During this treatment, the drug will only nucleate with extreme difficulty. If the solute commences to nucleate and microcrystals form, the particle size will be very small due to the extremely high viscosity of the medium at this low temperature and the short time interval for the completion of solidification.

The solidification time may play an important factor especially in obtaining a metastable solid solution (21). It is also axiomatic that crystal size will be smaller if the crystallization takes place in a short time interval. This principle should also hold for the solidification of the PEG-drug melt systems. Therefore, in order to obtain a metastable solid solution or fine particle size of the drug precipitated in the PEG-drug solid dispersion form, the melt should be cooled to the solid state as fast as possible. It should be emphasized that this does not apply to the true or thermodynamically stable solid solutions. Although the precipitation of the metastable or supersaturated solid solutions of PEG-drug systems may occur, this process is usually sluggish (21). As will be discussed in a later communication, the key to the complete absorption of gris is the well-dispersed and wetted "colloidal" particles. The same principle should also apply to all other drugs. Therefore polyethylene glycols may well be ideal matrices for most water-insoluble drugs (assuming they are soluble in the PEG melt) whether they form stable or metastable solid solutions or fine particles of pure drugs dispersed in the matrix.

As discussed above, PEG-drug solid dispersion forms can be simply prepared by directly melting their physical mixtures. Although many drugs may decompose at their melting points, they may be stable 50 or 100° below their melting points and it is possible to dissolve smaller amounts of the drug in the PEG melt below its decomposition point. Under such conditions, this direct melting method should be more convenient and economical than the solvent method proposed by Tachibana *et al.* (13) and Mayersohn *et al.* (11). The direct melting method cannot be applied to the polymers previously suggested by these authors because of their high melting points and/or thermal instability (17). Polymers of PEG also possess an advantage when the use of the solvent method is required when using drugs which are thermally unstable, because the PEG polymers are very soluble in a broad spectrum of organic solvents including ethanol, chloroform, *N,N*-dimethylformamide, and dimethylsulfoxide. Furthermore, the systems of PEG-drug-solvent will become increasingly viscous as the solvent evaporates. It should be noted that high vacuum can be applied to facilitate the

Table I—Twenty, Fifty, and Seventy Percent Dissolution Times for Various Forms of Griseofulvin in Saturation Dissolution Apparatus[a]

Physical forms of Gris	T_{20}, min.	T_{50}, min.	T_{70}, min.
100–200 Mesh pure Gris	> 60.0	—	—
Micronized Gris (nonwetted)	25.0	- -	—
Micronized Gris (wetted)	2.0	30.0-40.0	—
5% Gris-PEG 6000	≪ 1.0	0.3	1.5
10% Gris-PEG 6000	≪ 1.0	0.5	3.0
20% Gris-PEG 6000	≪ 1.0	3.0	15.0
40% Gris-PEG 6000	< 1.0	14.0	—
5% Gris-PEG 4000	≪ 1.0	0.3	2.0
5% Gris-PEG 20,000	≪ 1.0	0.6	2.5
20% Gris-PEG 20,000	≪ 1.0	4.0	—
7.5% Gris-pentaerythritol	≪ 1.0	0.5	4.0
20% Gris-pentaerythritol	< 1.0	3.8	15.0
10% Gris-Pentacrythrityl tetraacetate	< 1.0	8.0	- -
10% Gris-succinic acid	1.2	10.0	50.0
5% Gris-citric acid	≪ 1.0	0.2[b]	0.3[b]
20% Gris-citric acid	≪ 1.0	1.0	5.0

[a] Five milligrams Gris in 500 ml. of water at 25°. [b] Dissolution times taken from recorded absorbance readings. Values are not corrected for the circulation lag time of approximately 15 sec.

removal of organic solvents with higher boiling points at the lower temperature especially if the last two solvents are used.

The use of PEG polymers has other advantages. These polymers, especially PEG 1500, 4000, and 6000, are almost spectroscopically transparent in the visible and UV regions; therefore assays and dissolution rate studies of PEG-drug solid dispersions can be undertaken directly and easily by the simplest visible or UV absorbance method without resorting to the extraction procedure.

Pentaerythritol—It is well known that globular or plastic compounds will form a wide range of solid solutions above their plastic points. For example, pairs of cyclopentane-2,2-dimethylbutane (19) and chemically unrelated methane and argon (22) form continuous solid solutions at appropriate temperatures. The reasons for their mutual solubility are the similarity in their symmetry and almost free rotation (hence low lattice energy) above their plastic points. Since plastic compounds have the lowest lattice energy and strain, it is reasonable to expect that they will more easily accommodate all kinds of molecules in their crystal lattice for the formation of solid solutions. Pentaerythritol, a typical globular compound (19), was selected for the test of this possibility. Its transition point from the tetragonal Crystal II to the cubic, plastic Crystal I is 185° with an entropy of transition of 22.8 cal. deg.$^{-1}$ mole^{-1}. The Crystal I melts at 260° with a typical low entropy of fusion of 3.2 cal. deg.$^{-1}$ mole^{-1}. Although the pentaerythritol is water-soluble (1 g. in 18 ml. of water at 15°), its solubility in organic solvents is quite limited. Preparations of solid solutions utilizing the organic solvent method are therefore difficult and force one to use the direct melting method. Due to its high melting point, it is clearly not a useful carrier for thermal-labile compounds.

Pentaerythrityl tetraacetate—Pentaerythrityl tetraacetate probably has plastic properties due to its tetrahedral structure, although thermodynamic data are not available. It is fairly water-soluble (23). It has a low melting point, 80–82° and is also soluble in certain organic solvents such as ether, ethanol, and other chemicals. Therefore, the solid dispersion of drugs in this carrier can be easily prepared by the direct melting and/or the solvent methods.

Citric Acid—Citric acid (a normal metabolic constituent of animals), a tricarboxylic acid, has been found by the authors to be capable of glass formation. Although succinic acid, a dicarboxylic acid, has similar physicochemical properties as citric acid, it does not exhibit this particular property. The melt of succinic acid was found to solidify rapidly on cooling, while that of citric acid goes through a viscous state and solidifies less rapidly. After standing at 37° for a few days, a hard, brittle, and transparent glass solution can be obtained. Glass solution formation was also found in the systems of citric acid-phenobarbital and citric acid-hexobarbital. In the glass solution, the active drug is dispersed molecularly in the matrix of the carrier.

There is usually a relatively strong chemical binding between the solute and the solvent in the solid solution (24), while the lattice

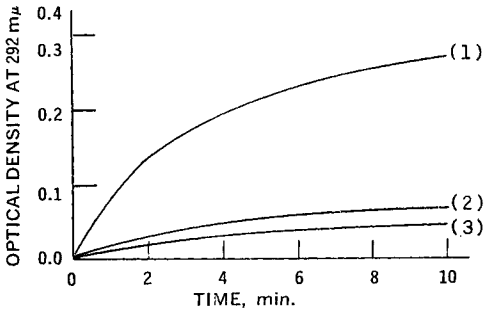

Figure 1—*Griseofulvin dissolution rate studies, 5 mg./500 ml. water at 25°. Key: (1) wetted, micronized Gris powder; (2) nonwetted, micronized powder; (3) 100-200 mesh powder. (Maximum optical density 0.7.)*

energy in the glass solution is much less because of its similarity to the liquid solution. Therefore, the dissolution rate of drugs in the glass solution should be theoretically faster than that in the solid solution.

Citric acid is very water-soluble, but unfortunately insoluble in most organic solvents. Therefore systems of citric acid-drug can only be prepared by the direct melting method. The melting point of anhydrous citric acid is 153°, while that of the monohydrate form is only about 100°. Both forms of citric acid decompose about 165° (22). It seems logical, therefore, that the monohydrate rather than the anhydrous form should be used in the preparation of solid dispersion of drugs. Gris was found to be partially decomposed during the melting process with anhydrous citric acid (see below). The potential use of monohydrous citric acid with gris and other drugs remains to be further investigated.

Stability Studies—*Pure Gris*—Although the melt and solidified mass of pure gris appear slightly discolored,[5] the slight degree of decomposition could not be detected by the various physical methods employed in this study. For example, the melting point, the spectra of the UV, IR, and fluorescence are all ostensibly identical

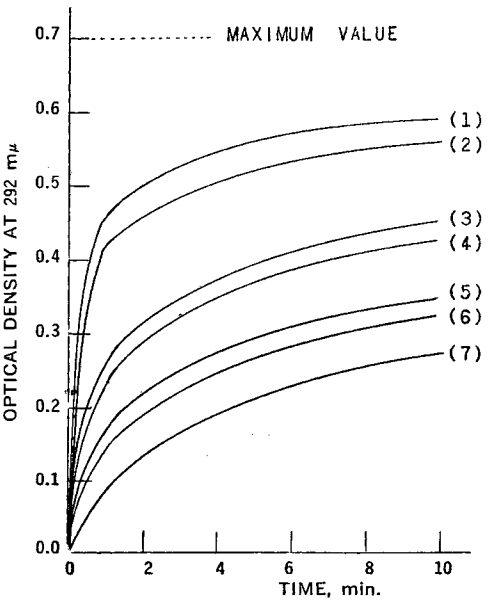

Figure 2—*Griseofulvin dissolution rate studies, 5 mg./500 ml. water at 25°. Key: (1) 5% Gris-PEG 6000; (2) 10% Gris-PEG 6000; (3) 20% Gris-PEG 6000; (4) 10% Gris-PEG 6000 prepared by ethanol method; (5) 20% Gris-PEG 6000 prepared by ethanol method; (6) 40% Gris-PEG 6000; (7) wetted micronized powder.*

[5] Poole (26) reported that the discoloration of the melt of griseofulvin-isogriseofulvin mixture when heated to 210 to 230° can be avoided by forming a blanket of nitrogen over the apparatus during the heating process.

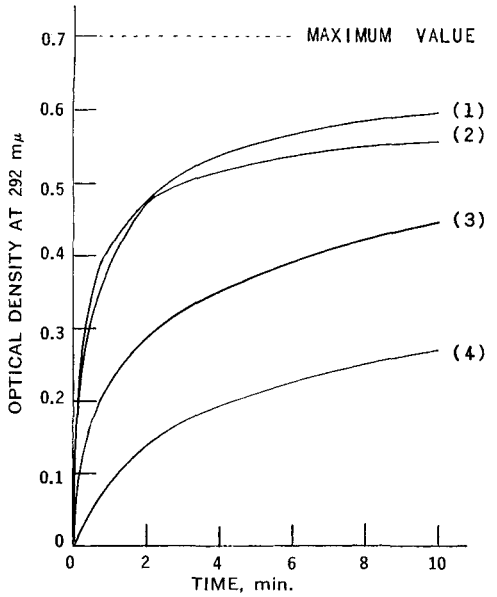

Figure 3—*Griseofulvin dissolution rate studies, 5 mg./500 ml. water at 25°. Key: (1) 5% Gris-PEG 20000; (2) 5% Gris-PEG 4000; (3) 20% Gris-PEG 20000; (4) wetted, micronized Gris.*

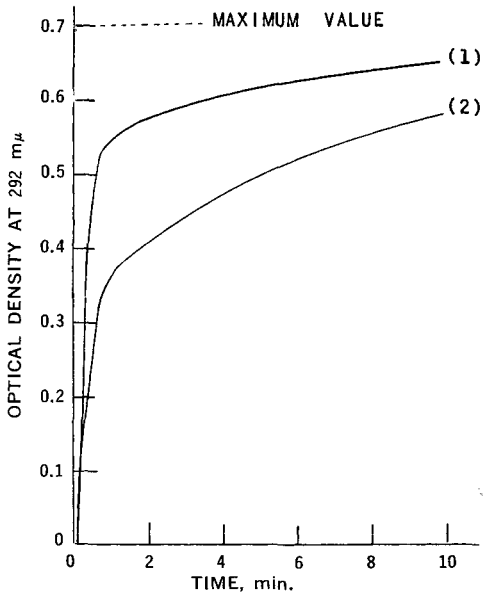

Figure 5—*Griseofulvin dissolution rate studies, 5 mg./500 ml. water at 25°. Key: (1) 5% Gris-citric acid; (2) 20% Gris-citric acid.*

to those of unheated gris. No new spots were detected by TLC. The thermal stability of gris is further supported by the finding of Sekiguchi *et al.* (25). In their differential thermal analysis study, no thermal effect below its melting point was observed. In their thermogravimetric analysis study, no detectable change in weight of gris was found when heated up to 240°. From the above evidence, it can be concluded that essentially gris is thermally stable and the decomposition after the rapid heating to its melting point or slightly beyond its melting point is negligible.

Gris Dispersed in Polyethylene Glycol Polymers—Gris dispersed in these polymers prepared either by the direct melting or the solvent method showed the identical UV and fluorescent spectra on a mass basis as that of pure gris. In addition, no new spots could be detected on the thin layer plate. On the basis of these facts, it seems gris is also not decomposed by the processing. It should be noted that if a high concentration of gris (*e.g.*, 20–40% gris) is incorporated in the melt, a high temperature is required and the resulting solid was slightly brown in color, and its color became darker as the time of heating was prolonged. It seems likely the discoloration of gris-PEG melt might have been prevented by blowing nitrogen over the apparatus during the heating process.[5] It should be noted that the Gris dispersed in PEG 6000 by the solvent method was colorless.

Gris Dispersed in Pentaerythritol—The gris, 7.5 and 20% (w/w) dispersed in the pentaerythritol by the direct melting method also showed an identical ultraviolet spectra as the pure compound. However, the deviation of the UV spectra and extra spots on the thin-layer plate were found in the samples when they were prepared in larger quantities (above 10 g.) and required longer time of heating at high temperature (above 235°). Only samples without decomposition were used for the dissolution rate study.

Gris Dispersed in Pentaerythrityl Tetraacetate—The melts of 5 or 20% (w/w) of gris in the system of gris-pentaerythrityl tetraacetate were colorless. The Gris dispersed in this carrier showed the same UV spectra and the same R_f value (single spot only) as pure com-

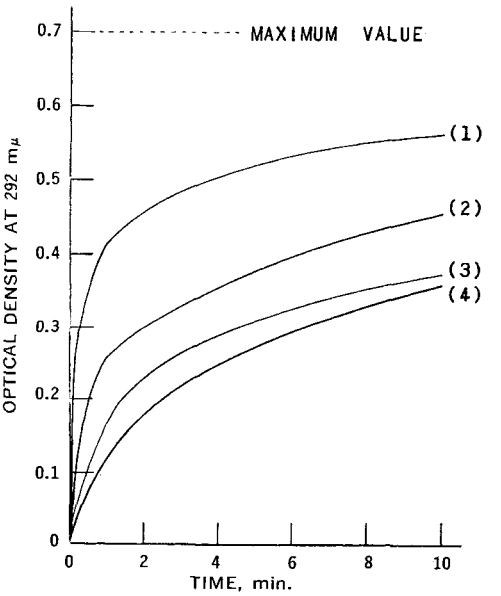

Figure 4—*Griseofulvin dissolution rate studies, 5 mg./500 ml. water at 25°. Key: (1) 7.5% Gris-pentaerythritol; (2) 20% Gris-pentaerythritol; (3) 10% Gris-pentaerythrityl tetraacetate; (4) 10% Gris-succinic acid.*

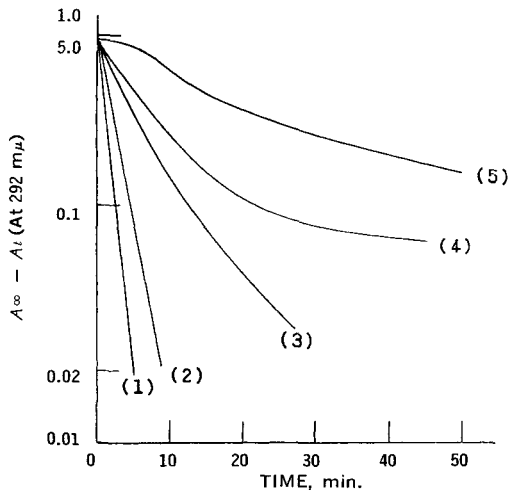

Figure 6—*Griseofulvin dissolution rate data (amount remaining to be dissolved) from 125 mg. in 18 l. of water at 36.7°. Key: (1) 10% Gris-PEG 6000; (2) 20% Gris-PEG 6000; (3) 40% Gris-PEG 6000; (4) wetted, micronized Gris; (5) nonwetted, micronized Gris.*

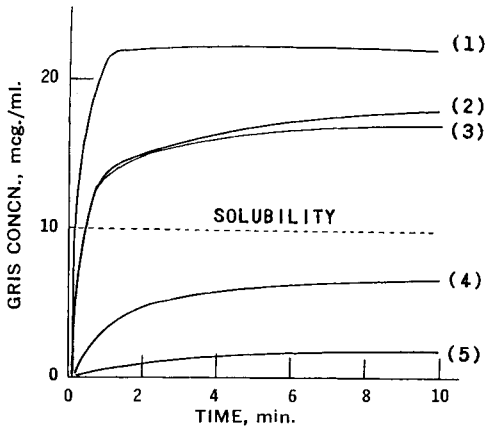

Figure 7—*Dissolution rate plots of Griseofulvin in 500 ml. water at 25°. Key: (1) 10% Gris-PEG 20000 (25 mg. Gris used); (2) 5% Gris-PEG 4000 (25 mg.); (3) 7.5% Gris-pentaerythritol (15 mg.); (4) pure wetted, micronized Gris (15 mg.); (5) pure nonwetted, micronized Gris (15 mg.).*

pound. These data indicate that gris is not decomposed by the processing. It should be noted that the melting point of this carrier is only 80–82°.

Gris Dispersed in Citric Acid—The gris was found to be partly decomposed when heated together with citric acid below 160° as shown by the deviation of the UV spectra in certain regions. About 20–30% acidic decomposition product was found. The extent of the possible conversion of gris to isogriseofulvin (due to the acidity) during the fusion processing with anhydrous citric acid was not determined.

Dissolution Rate Studies—Table I and Figs. 1–5 include data obtained in the 500-ml. dissolution apparatus under conditions in which the solution is approaching saturation. Indeed if carried to completion, a saturated solution would result. Table I compares the studies utilizing the time it took for each preparation to reach 20% dissolution (T_{20}), 50% dissolution (T_{50}), and 70% dissolution (T_{70}). Figure 6 shows the data obtained from the studies of 125 mg. gris in 18 l. of distilled water. Figure 7 shows the results of dissolution rate when excess amounts of gris were studied in 500 ml. of distilled water.

Pure Gris—The dissolution rate of the nonwetted, micronized gris is markedly slower than that of the same powder when wetted first prior to study (with 2 ml. of 0.2% polysorbate (Tween 20) solution as shown in Table I, Figs. 1 and 7. Furthermore, the unwetted sample has almost the same dissolution rate as the specially prepared 100–200 mesh (Fig. 1). This indicates the serious agglomeration problem inherent with water-insoluble drugs such as gris. Therefore, unless steps are taken to assure appropriate dispersion and wetting, the administration of the micronized or fine particles of drugs may not produce the expected effect.

Dispersion in PEG's—The strikingly fast dissolution rates of gris dispersed in PEG systems are shown in Table I, Figs. 2, 3, 6, and 7. Even the preparation containing 40% of gris in the system of gris-PEG 6000 (designated by 40% gris-PEG 6000) possesses faster dissolution rate than the wetted, micronized gris. Hence, this rapid dissolution may be attributed by the molecular and/or colloidal dispersion of gris in the carrier matrix as discussed above. Owing to the similar physical and chemical properties of PEG 4000, 6000, and 20,000, it is understandable that gris dispersed in these three carriers all exhibit approximately the same dissolution characteristics. Another factor which might also contribute to the fast dissolution and the easy attainment of supersaturation (Fig. 7) is the increased solubility of gris in the fluids of the diffusion layer. While the solubility of gris in water at 25° is 10 mcg./ml., it is approximately 25,000 mcg./ml. in pure PEG 4000 and may show the same order of solubility in the higher molecular weight polymers. It is also interesting to note that the dissolution rate data of the 10 and 20% gris-PEG 6000 mixtures run in 18 l. of water are monoexponential beyond 90% dissolution (Fig. 6).

The dissolution rates of the 10 and 20% gris-PEG 6000 mixtures prepared by the solvent method are much slower than those prepared by the melting method, as shown in Fig. 2. This evidence, as well as the fact of limited solubility of gris in PEG, supports the contention that the systems of gris-PEG prepared by direct melting and fast solidification are in thermodynamically metastable state. However, the dissolution rate of 10% gris-PEG 6000 was found unchanged even after 6 months of storage at room temperature. This indicates the transformation in such systems may be very slow.

Dispersion in Globular Carriers and Glass Solution—The dissolution rates and the attainment of supersaturation of gris dispersed in globular carriers such as pentaerythritol and pentaerythrityl tetraacetate are shown in Table I and Figs. 4 and 7. Although the phase diagram of these systems has not been determined, the fast dissolution and the attainment of supersaturation of gris dispersed in these carriers are compatible with the postulate that they exist in the form of solid solutions. The potential application of soluble globular compounds as carrier systems in increasing dissolution and oral absorption remains to be further investigated. It should be noted that the dissolution rates of gris dispersed in the above carriers are faster than that of gris dispersed in succinic acid as proposed by Goldberg. The dissolution of gris dispersed in citric acid glass solution shows the fastest rate among the solid dispersion forms studied (Fig. 5). Although partial decomposition of gris was noted during the fusion process, the fastest dissolution rate obtained from such a system warrants further study in the future.

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ACKNOWLEDGMENTS AND ADDRESSES

Received June 4, 1969 from the *School of Pharmacy, University of California, San Francisco Medical Center, San Francisco, CA 94122*

Accepted for publication August 26, 1969.

Abstracted from a dissertation submitted by Win Loung Chiou to the Graduate Division, University of California, San Francisco Medical Center, in partial fulfillment of Doctor of Philosophy degree requirements.

This research was supported in part by a grant-in-aid from the research funds of the Academic Senate, San Francisco Division, University of California. The information disclosed in this paper is proprietary to the Regents of the University of California.

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The Amino Acid Nature of Ampicillin and Related Penicillins

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Abstract □ The amphoteric penicillins, ampicillin and Wy-4508 (cyclacillin), possess properties similar to the alicyclacillinphatic amino acids. At a pH equal to the isoelectric point (pI) they exist essentially as zwitterions (dipolar ions), and in this form are most stable and least soluble in water. The aqueous solubility of ampicillin changes only slightly with a change in ionic strength unless a nonpolar solvent is added. In water at 25°, the carboxyl groups of all penicillins appear to have the same pK_1 (2.6–2.7), while the amino groups of the amphoteric penicillins vary in the pK_2 values over a wide range (7.24–7.65), probably being influenced by the adjacent side chin groups. A change in the dielectric constant affects the pK_1 more than the pK_2; a change in temperature does the opposite. The formation of ampicillin zwitterions from its uncharged species is an exothermic reaction, and the heat of formation is about 10.7 kcal./mole.

Keyphrases □ Ampicillin, related penicillins—amino acid similarities □ pH–stability profile—penicillins □ Amphoteric penicillins in solution—apparent stability □ Physicochemical properties, penicillins—biological activity relationship

Ampicillin (6-[2-amino-2-phenylacetamido]penicillanic acid) was first prepared by Doyle *et al.* (1) in 1961. After extensive antimicrobial and pharmacological evaluations, this antibiotic was shown to be very acid-stable (2), well absorbed (3–5), and effective at low minimal inhibitory concentration (MIC) against a wide variety of Gram-negative as well as Gram-positive organisms (5–7). Wy-4508, an aminoalicyclic penicillin prepared by Grant *et al.* (8, 9), also has a broad antibacterial spectrum, and in addition has a higher ratio of *in vivo* to *in vitro* activity than ampicillin. Part of this superiority may be due to its high, prolonged blood concentrations and low serum binding (10). Ampicillin apparently owes its activity and stability to the presence of the free amino group at the α-position of the *N*-acyl side chain of the penicillin nucleus, since when this group is substituted or derivatives are made, the activity reverts to a more Gram-positive and lipophilic type (1). Recently, Cieslak and Wasilewa (11) reported that the presence of a free α-amino group, although required, is apparently insufficient for broad antimicrobial activity; the chemical nature of the penicillin side chain is also an essential factor.

Commonly used penicillins, both natural and semi-synthetic, such as pencillins benzyl-and phenoxymethyl, methicillin, dicloxacillin, and nafcillin are salts of monobasic *N*-substituted penicillanic acids. Ampicillin and Wy-4508, however, are ampholytes, *i.e.*, they behave as both acids and bases since they carry both carboxyl and amino groups at the ends of the molecules.

Austin *et al.* (12) reported the formation of ampicillin hydrates. Grant and Alburn (13) found the monohydrate form of ampicillin less stable than the anhydrate. Poole and Bahal (14) further studied the anhydrate-trihydrate phase transition. The authors recently reported on the chemical kinetics of ampicillin in solution (15). Now using ampicillin as a model, these studies have been extended to the solubility characteristics, dissociation behavior, and apparent heat of dissociation (ionization) in solution of these amphoteric penicillins.

EXPERIMENTAL

Penicillins—All the penicillins were products or new compounds of Wyeth Laboratories. Their purity was greater than 98%. The following were used: ampicillin (anhydrate), 6-(2-amino-2-phenylacetamido)penicillanic acid, Lot C-10575 and Lot 10959, m.p., 202-203° (dec.); Wy-4508 6-(1-aminocyclohexanecarboxamido)-penicillanic acid, Lot C-10789 (anhydrate) m.p., 182–183° (dec.); Wy-7953, 6-(1-aminocyclopentanecarboxamido)penicillanic acid, Lot C-10785, m.p., 188–189° (dec.); Wy-8542, 6-(1-amino-3-methylcyclopentanecarboxamido)penicillanic acid, m.p., 164-165° (dec.), (new compound); 6-APA, 6-aminopenicillanic acid, Lot C-11093, m.p., 187-189° (dec.); dicloxacillin sodium monohydrate, 6-[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolecarboxamido] penicillanic acid, sodium salt·H_2O, Lot C-10651; nafcillin sodium monohydrate, 6-(2-ethoxy-1-naphthamido) penicillanic acid, sodium salt·H_2O.

All other chemicals were commercially available reagent grade. The water used for penicillin solutions, titrants, and buffers was deionized, distilled and freshly boiled. The pH was 6.75 at 25°.

Procedures—To determine the solubility, an excess of each drug (about four times the amount needed for saturation) was added to each of a series of 120-ml. (4-oz.) bottles, followed by adding 50 ml. of solvent. The bottles were capped, placed in a constant-temperature bath, mechanically rotated for 2 hr., and allowed to stand about 30 min. at the appropriate temperature. Samples were taken from the supernatants and filtered through Millipore filters,[1] diluted with

[1] Millipore filters were type HA (aqueous solvent) and type LC (aqueous-organic solvent mixture).