Increasing Dissolution Rates and Gastrointestinal Absorption of Drugs *Via* Solid Solutions and Eutectic Mixtures II

Experimental Evaluation of a Eutectic Mixture: Urea–Acetaminophen System

By ARTHUR H. GOLDBERG*, MILO GIBALDI, and JOSEPH L. KANIG

The binary system of APAP and urea was found to be a simple eutectic mixture with negligible formation of solid solutions. Solubility studies indicated that urea increased significantly the solubility of APAP. Dissolution rate studies were conducted with APAP alone, and in fused and physical mixtures with urea. An unusual dissolution phenomenon was found to exist in the system and is considered. In all cases the presence of urea enhanced the dissolution rate of APAP by virtue of a microenvironmental solubilization. The fused mixture at the eutectic composition was found to give similar, but prolonged enhancement of dissolution rate as compared to the physically mixed sample.

It is well established that dissolution is frequently the rate-limiting step in the gastrointestinal absorption of a drug from a solid dosage form. The relationship between solution rate and absorption is particularly distinct when considering drugs of low solubility. Consequently, numerous attempts have been made to modify the dissolution characteristics of certain drugs in an effort to attain more rapid and more complete absorption.

Bruner and Tolloczko (1) were the earliest workers to demonstrate that dissolution rate was a function of the surface area exposed to the dissolution medium. Accordingly, a drug will dissolve more rapidly when its specific surface area is increased, *i.e.*, when its particle size is decreased.

Levy (2) has considered a number of methods by which a drug may be presented to the gastrointestinal fluids in finely divided form. The most direct method is the utilization of microcrystalline or micronized particles which may be administered in any one of a number of dosage forms. A second method involves the administration of solutions from which, upon dilution with gastric fluids, the dissolved drug will precipitate in the form of very fine particles. A more unique way of obtaining microcrystalline dispersions of a drug in gastrointestinal fluids has been recently suggested by Sekiguchi *et al.* (3, 4). This approach involves the administration of a eutectic mixture composed of the drug and a substance which dissolves readily in water.

Sekiguchi and co-workers (3, 4) have proposed that when the eutectic mixture is exposed to the gastrointestinal fluids, the soluble carrier dissolves rapidly, leaving the insoluble drug in an extremely fine state of subdivision. More recently Goldberg *et al.* (5) presented theoretical arguments which attempted to demonstrate that the results obtained by Sekiguchi (3, 4) were due to the formation of solid solutions rather than simple eutectic mixtures. The existence of solid solutions in the eutectic mixture precluded a direct evaluation of the role of particle size reduction in the enhancement of dissolution. Owing to the physical-chemical characteristics of a solid solution, a very rapid rate of dissolution is to be expected when an insoluble drug is dissolved in a soluble carrier (5).

The purpose of this investigation was to compare the dissolution rate of a *simple eutectic mixture*, composed of the drug and a readily dissolving substance, with the dissolution rate of the drug alone. A study of a eutectic mixture, uncomplicated by the presence of solid solutions, permits a more realistic evaluation of the utility of the eutectic system in enhancing dissolution.

EXPERIMENTAL

A study was initiated to find a poorly soluble drug that would form a simple eutectic mixture with a water soluble carrier. The carriers investigated met the following criteria: (*a*) soluble in water; (*b*) physiologically inert; (*c*) a melting point of not more than 200°; (*d*) thermal stability up to its melting point; (*e*) a relatively low vapor pressure.

A number of drugs were employed that met the following criteria: (*a*) poor water solubility; (*b*) therapeutically significant; (*c*) thermal stability up to its melting point; (*d*) relatively low vapor pressure; (*e*) melting point of not more than 250°.

Screening Procedure.—In order to select combinations which would lend themselves to more detailed investigation, an initial screening procedure

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was developed to permit rapid evaluation. Equal quantities (3 Gm.) of carrier and drug were physically mixed and placed, along with a thermometer, into a test tube. The tube was immersed into a temperature controlled silicone[1] bath, preset to the temperature of the melting point of the lower melting component. The mixture was constantly stirred to facilitate distribution of heat and the temperature of the silicone bath was slowly raised, if necessary, until complete melting occurred. The following observations were made during each such screening procedure: (*a*) temperature at which mixture started to melt; (*b*) temperature at which discoloration, gas evolution, or fumes occurred (if such phenomena did occur); (*c*) temperature at which complete melting was effected; and (*d*) the number of distinct phases present in the melted mixture.

The fused liquid was then immediately poured onto Ferrite plates[2] and the following evaluations made: (*a*) length of time for crystallization to occur; (*b*) physical state of mass (crystalline or amorphous); and (*c*) length of time required for the amorphous mixtures to change to a crystalline form.

Solid-Solid Interaction.—On the basis of results obtained in the screening procedure, the combination of APAP[3] and urea was selected for further study. This mixture formed a homogeneous liquid when fused, exhibited a melting point lower than that of the lower melting component, and recrystallized to a crystalline solid immediately upon quenching in air under ambient conditions.

A phase diagram of APAP–urea was made using the cooling curve method, employing blends of APAP and urea in the following mole fractions: 0.9–0.1; 0.8–0.2; 0.7–0.3; 0.6–0.4; 0.5–0.5; 0.4–0.6, and 0.2–0.8. The blended mixtures were placed into the inner tube of a Beckman molecular weight apparatus with the stirring loop, thermometer, and stopper in place. The tube was then immersed into a temperature controlled silicone bath. The temperature was slowly raised to effect fusion, and to allow the temperature of the melt to rise to about 10° above its melting point. The entire inner tube was then placed into the outer jacket of the Beckman apparatus which was immersed in a water bath maintained at 60°. The top of the stirring loop was attached to the arm of a U.S.P. tablet disintegration apparatus, which raised and lowered the stirring loop at the rate of 30 times per minute within the fused drug-carrier combination.

During the cooling process, temperature was plotted *versus* time, and two discontinuities in the curve were noted. The first change of slope (at the higher temperature) is comparable to the melting point of that component in the mixture which is in excess of the eutectic composition, and the second change in slope (at the lower temperature) corresponds to the eutectic temperature. The critical temperatures thus obtained were plotted *versus* composition on a second graph.

A second phase diagram of urea–APAP was prepared using a microthermal technique.[4] Various ratios of the materials were weighed, intimately mixed, and placed on a microscope slide. The slide was covered with a cover slip, and sealed with silicone grease,[5] to minimize any possible loss due to sublimation. This preparation was heated until fusion occurred, and then allowed to cool. The cooled crystalline mass was then reheated at the rate of 4°/min. by means of a heating stage attached to a microscope fitted with polarizing lenses. Using 100 magnification power, observations were made of the melt.

The first change noted occurs at the eutectic temperature. At this point the solid appears to disappear partially, and small liquid areas become apparent. These areas of liquid continue to increase in size until all of one component dissolves in the eutectic melt. The crystals remaining constitute that component which is present in excess of the eutectic composition. As the temperature increases, the component in excess slowly disappears from view. The temperature at which the last bit of crystal disappears is taken as the melting point of the component in excess. A phase diagram was constructed by plotting both temperatures (where melting first appears, and the final melting point) *versus* ratio of components (per cent w/w).

Interaction in Aqueous Solution.—To determine any possible interaction between drug and carrier in aqueous solution, solubility studies were performed. An excess amount of drug was placed in 60-ml. test tubes equipped with screw caps and containing 30 ml. of an aqueous solution of the carrier in varying concentrations. The content of each tube was equilibrated at 37° in a Gyrotory incubator shaker.[6]

At the end of this period, 1-ml. samples were withdrawn by means of a filter pipet. Each milliliter was diluted to 100 ml. with water, and 0.5 ml. of this dilution was added to 0.5 ml. of distilled water, and diluted to 10 ml. with acidified methanol (1% v/v solution of 0.1 *N* HCl in methanol). The absorbance of each diluted sample was determined at 242 mμ using a recording spectrophotometer.[7] A blank of 10% water in acidified methanol was employed. The absorbance was read and the amount of APAP present was determined by dividing the absorbance by the slope (obtained by the method of least squares) of a previously constructed Beer's law curve. Preliminary investigation had indicated that urea in no way interfered with the assay procedure.

Dissolution Studies.—The dissolution studies were conducted using the tape method (6). This method employs a strip of plastic adhesive,[8] tautly affixed to a metal frame. The powdered sample to be evaluated is dusted on the adhesive surface in a monoparticulate layer. The entire frame is then immersed below the surface of the dissolution medium which is stirred by a paddle attached to an overhead, constant speed motor rotating at 53.5 r.p.m.

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[1] 550 Fluid, Dow Corning Corp., Midland, Mich.

[2] 10 × 14 in., chrome plated, Apollo Co., Inc., New York, N. Y.

[3] A common synonym for acetaminophen or *N*-acetyl-*p*-aminophenol.

[4] The authors gratefully acknowledge the expert assistance of Miss Marie Jones, microscopist, Bristol-Myers Division, Hillside, N. J., in this phase of the work.

[5] Hi-vacuum grease, Dow Corning Corp., Midland, Mich.

[6] Model G-25, New Brunswick Scientific Co., New Brunswick, N. J.

[7] Model DB, Beckman Instrument Co., Mountainside, N. J.

[8] Scotch Brand Magic Mending Tape, 3/4 in. wide, Minneapolis Minnesota Mining Co., Minneapolis, Minn.

TABLE I.—APAP SAMPLES EMPLOYED IN DISSOLUTION STUDIES

Sample	Compn., mg. APAP	Urea	Mesh Size	Method of Prepn.
1	30	...	50–60	Fusion
2	30	...	100–120	Fusion
3	30	23.8	50–60	Fusion
4	30	23.8	50–60	Physical mixture
5	30	35.7	50–60	Physical mixture

Table I lists the various APAP samples used in the dissolution studies. Samples 1–3 were prepared by fusing APAP or a blend of APAP and urea. When complete liquefaction occurred, the homogeneous melt was immediately cast on Ferrite plates under ambient conditions. The congealed solid was then crushed using a mortar and pestle. The resulting powder was subsequently classified by means of a Syntron shaker operated at 90 v. for 2 min. The desired fraction was then collected. Samples 4 and 5 were prepared by first fusing, congealing, and sizing the individual components and then blending the two materials in the indicated proportions.

The dissolution fluid consisted of 400 ml. of distilled water maintained at 37° in a 600-ml. beaker which was immersed in a constant-temperature water bath. The particles to be tested were weighed and dusted onto the tape. The frame was then positioned in the dissolution apparatus and, at time zero, dropped below the surface of the dissolution fluid. One-milliliter samples were withdrawn at 1-min. intervals for 5 min. Each sample was diluted to 10 ml. with acidified methanol and assayed spectrophotometrically as previously outlined.

RESULTS AND DISCUSSION

Solid-Solid Interactions.—The phase diagrams obtained by the cooling curve method and the microthermal technique closely coincided. An analysis of the phase diagram presented in Fig. 1 (which was prepared by the microthermal technique) reveals the existence of a binary system which closely approximates a theoretical eutectic mixture. No solid solubility was detected. Figure 1 shows the eutectic composition to be 52% APAP and 48% urea, and the eutectic temperature to be 115°.

The phase diagram prepared by the cooling curve method indicated a eutectic composition of 55.7% APAP and 44.3% urea. The eutectic temperature was found to be somewhat lower (110°) than the temperature observed when employing the microthermal technique. This finding is probably the result of supercooling. The small discrepancy in eutectic composition between each method of phase diagram preparation is attributable to the sublimation of urea from the open system employed in the cooling curve technique.

Interaction in Aqueous Solution.—Equilibrium solubility experiments were conducted to determine the extent of interaction between drug and carrier in solution. As may be noted in Fig. 2, urea was found to interact strongly with APAP in aqueous solution. This interaction was manifested by a linear increase in the solubility of APAP to the

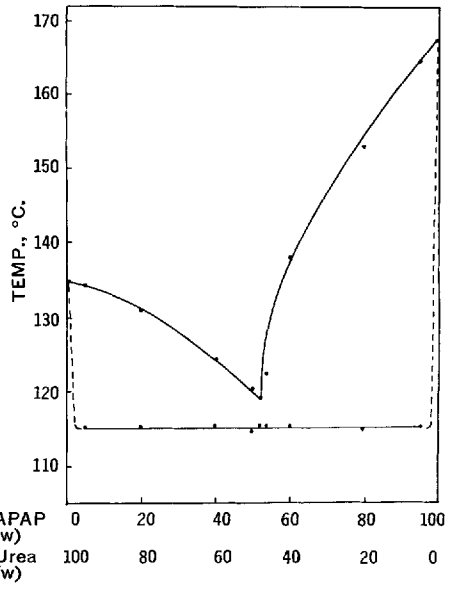

Fig. 1.—Phase diagram for urea–APAP system prepared by a microthermal technique.

extent of 0.23 Gm./Gm. of urea. The significance of the solubilization effect will be considered in the discussion of dissolution rates which follows.

Dissolution Studies.—According to the Noyes-Whitney equation, the dissolution rate of a solid is a function of the surface area presented to the dissolution medium as well as the concentration gradient existing between the solid–liquid interface and the bulk of the dissolution medium (7). Under conditions of constant surface area, as is observed in the dissolution of a material from a planar surface, the dissolution rate should follow zero-order kinetics

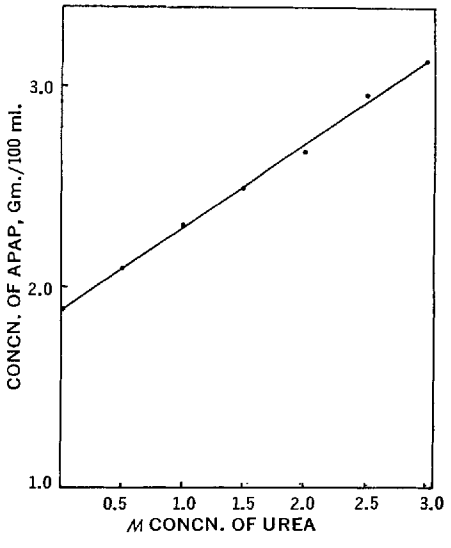

Fig. 2.—Aqueous solubility of APAP as a function of urea concentration.

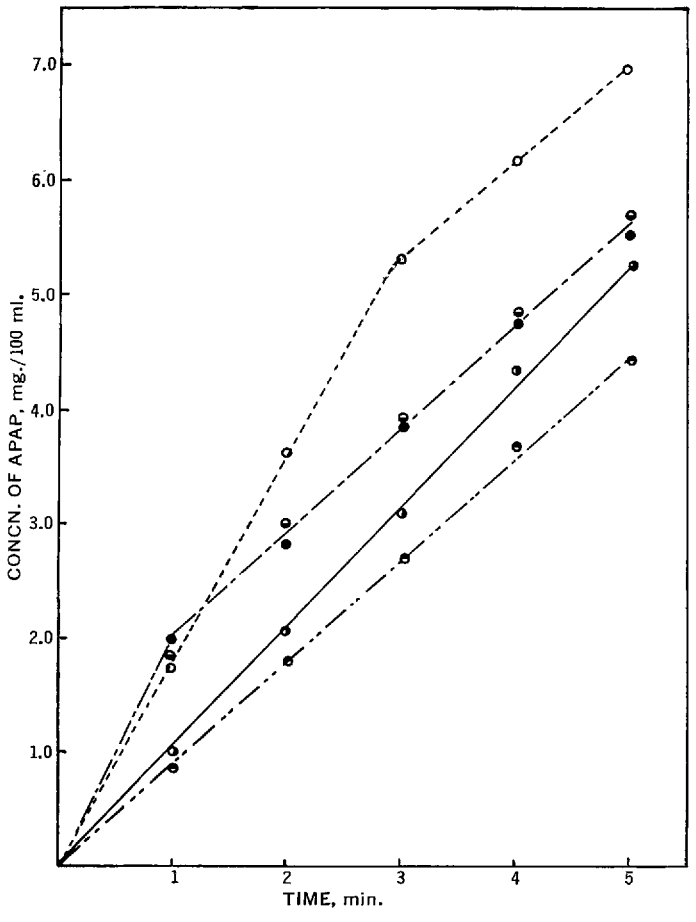

Fig. 3.—Dissolution rates of APAP and APAP–urea as determined by the tape method. Key: ◓, APAP, 50 60 mesh; ◑, APAP, 100–120 mesh; ●, APAP–urea, physical mixture at eutectic composition; ◒, APAP–urea, physical mixture, urea present in excess of eutectic composition; O, APAP–urea, fused eutectic.

provided the concentration gradient is maintained essentially constant by keeping the dissolution medium sufficiently dilute. On the other hand, in those situations where only the concentration gradient may be maintained constant, *e.g.*, in particulate dissolution, the dissolution rate is proportional to the surface area. Accordingly, the dissolution of particulate solids has been found to adhere to the "cube root law" which represents a mathematical model to account for the decrease in surface area during the dissolution process (8).

The results of the dissolution studies in this investigation appeared to differ considerably from theoretical expectations. Previous studies (6), utilizing the tape method, showed reasonable agreement with the "cube root law" indicative of particulate dissolution. Dissolution of the APAP samples, however, seemed to agree with a planar surface dissolution model. As may be noted in Fig. 3, dissolution curves were of two distinct types: either linear for the entire experimental period or biphasic, consisting of two linear segments. Both samples of pure APAP followed pseudo-zero kinetics over the 5-min. period. When the data obtained with the pure APAP were tested for fit to the "cube root law," it was found that the coarser sample (50–60 mesh) showed reasonably good agreement while the 100–120 mesh sample demonstrated significant curvature and deviation. Based on these observations, it was concluded that particulate density, *i.e.*, the number of particles per unit area of tape, exerted an influence on the dissolution process.

It has been theorized that the dissolution process involves the formation of a thin layer or film of saturated solution at the solid-liquid interface and the diffusion of molecules from this layer to the bulk solution (1). Applying this concept to the dissolution of particulates from the tape, it is apparent that as long as the particles are farther apart than the thickness of the diffusion layer, the "cube root law" would be obeyed. However, if the particulate density is increased so that the diffusion layer of each particle "overlaps" with that of its neighboring particle, it is reasonable to expect dissolution to approach a planar surface model. The latter situation was observed with the 100–120 mesh APAP.

When particles of pure APAP were physically mixed with particles of urea, a biphasic dissolution curve was obtained (Fig. 3). Theoretically, in a system measuring only particulate dissolution the urea would not influence the dissolution rate of the APAP since each particle would dissolve independently. However, the initial dissolution rate of APAP (from time zero to 1 min.) from both physically mixed samples was significantly greater than the dissolution rate of APAP alone. These findings further support the possibility that the diffusion layers of the urea and APAP particles

"overlap." When the sample is first introduced into the dissolution medium, the urea rapidly goes into solution and quickly attains a very high microenvironmental concentration in the "mixed" diffusion layer of both particles. The presence of urea increases the solubility of APAP in the diffusion layer and thereby increases the dissolution rate of the drug. When the eutectic mixture was studied, a biphasic dissolution curve again resulted, demonstrating an increased initial dissolution rate of APAP.

These findings coupled with the results obtained with the pure APAP samples indicate that the dissolution process, under these experimental conditions, adheres to a mixed mathematical model, *i.e.*, intermediate to a planar surface dissolution model and a particulate dissolution model. This rather unusual situation does not, however, negate the value of the system for comparing the relative dissolution rate of APAP from the various samples. In each case, with the exception of the pure APAP (100–120 mesh), the quantity of the drug, the particle size of the sample, and the approximate monolayer density were maintained constant. Moreover, the mechanism of dissolution remained the same regardless of the sample tested, as manifested by the pseudo zero-order kinetics observed in part or *in toto* in each dissolution run. It should nevertheless be noted that the use of the tape method for determining true particulate dissolution is dependent on maintaining a small monolayer area in relation to the area of tape on which the particles are placed.

The results of the dissolution studies permitted the calculation of pseudo zero-order rate constants. (Table II.) The pure APAP sample (50–60 mesh) yielded a rate constant of 0.89 mg./min. while the 100–120 mesh sample of pure drug showed a rate constant of 1.07 mg./min., showing an increase of approximately 20%. The physically mixed sample of APAP and urea, corresponding to the eutectic composition, demonstrated an initial rate constant (0–1 min.) of 1.99 mg./min., about twice that of pure APAP of comparable particle size. The second phase of this dissolution curve showed a rate constant of 0.90 mg./min. This second rate constant is the same as that of pure APAP of equal particle size (0.89 mg./min.). This suggests that urea has left the microenvironment at about 1 min. Verification of this conclusion was provided by microscopic examination of the sample; after 1 min., the tape is depleted of urea and only APAP particles remain.

When the amount of urea in the physically mixed sample is increased beyond the eutectic composition an initial rate constant (0–1 min.) of 1.85 mg./min. is found, comparing favorably to the initial rate constant found with the other physically mixed sample. The second phase of the dissolution (1–5 min.) had a rate constant of 0.83 mg./min., again quite close to that of pure APAP of equal mesh size. The urea concentration in the mixed diffusion layer is apparently close to the saturation level since initial dissolution rates were essentially independent of the quantity of urea in the sample. In addition, once the urea is completely depleted from the diffusion layer, APAP particles of equal size remain on the tape and dissolution is identical to the dissolution of pure APAP.

The fused eutectic mixture shows an initial rate constant (0–3 min.) of 1.72 mg./min., reasonably close to the initial rate constants found with the physically mixed samples. The second phase of the dissolution curve yielded a rate constant of 0.81 mg./min., again in close agreement with the rate constant of pure APAP particles of 50–60 mesh.

These results indicate that particle size reduction of APAP by eutectic formation with urea does not increase the dissolution rate of the drug. It has been observed in the present dissolution system that decreasing the particle size 50% yields a 20% increase in the dissolution rate of APAP. According to Findlay (9), the APAP in the eutectic should appear as fine-grained crystals. However, no evidence of any significant particle size reduction was observed. The initial rate of dissolution of APAP from the eutectic was found to be the same or slightly less than that of the physical mixture. The major difference between the physical mixture and the eutectic was one of duration of effect. It apparently required a longer period for the urea to diffuse completely from the eutectic than from the physical mixture, thereby increasing the duration of the solubilizing effect of the urea on the APAP.

Table II.—Pseudo Zero-Order Dissolution Rate Constants for APAP Alone and in Fused or Physical Mixtures with Urea

Sample	Description	Initial Rate Constant	Time Interval, min.	Second Rate Constant	Time Interval, min.
1 APAP	Fused, 50–60 mesh	0.89	0–5	...	...
2 APAP	Fused, 100–200 mesh	1.05	0–5	...	...
3 APAP–urea	Fused mixture, eutectic composition	1.72	0–3	0.81	3–5
4 APAP–urea	Physical mixture, eutectic composition	1.99	0–1	0.90	1–5
5 APAP–urea	Physical mixture, urea present in excess of the eutectic composition	1.85	0–1	0.83	1–5

A second major reason for believing that particle size reduction was not achieved in the eutectic is provided by the second rate constant, which approximated the rate constant for the 50–60 mesh APAP. This result suggests that the urea is leached from the mixed eutectic particle leaving a matrix of APAP with an effective surface area comparable to that of a 50–60 mesh particle of APAP. Therefore, the value of eutectic formation as a means of enhancing dissolution rate still remains somewhat dubious. An enhancement of dissolution rate by virtue of simple eutectic formation alone is yet to be demonstrated.

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Increasing Dissolution Rates and Gastrointestinal Absorption of Drugs *Via* Solid Solutions and Eutectic Mixtures III

Experimental Evaluation of Griseofulvin–Succinic Acid Solid Solution

By ARTHUR H. GOLDBERG*, MILO GIBALDI, and JOSEPH L. KANIG

The phase diagram for the griseofulvin and succinic acid system showed a eutectic mixture with considerable solid solubility of griseofulvin in succinic acid. Evaluation of the dissolution rates of critical samples indicated that the solid solution dissolved 6.5–7 times faster than the pure material.

THE UTILIZATION of finely subdivided or micronized particles as a means of increasing the rate of dissolution of a drug has been considered frequently (1–4). Various methods of achieving particle size reduction have been reviewed by Levy (5). Sekiguchi *et al.* (6, 7) have suggested that particle size reduction, as a means of increasing gastrointestinal absorption of a drug, may be achieved through eutectic formation between a poorly soluble drug and a rapidly soluble carrier. Goldberg *et al.* (3, 4) have proposed that the increased absorption and dissolution rates found by Sekiguchi *et al.* were a function of the solid solutions present in the samples tested, rather than eutectic formation *per se*. Goldberg *et al.* (3) have also noted that the dissolution rate of a poorly soluble drug from a solid solution with a soluble carrier should be considerably faster than any other physical form of the drug, including the soluble eutectic and micronized forms. The purpose of this study was to evaluate experimentally the role of solid solutions in increasing dissolution rates.

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EXPERIMENTAL

The experimental procedures for selection of drugs and carriers, including the initial screening techniques, were reported previously (4). The system selected for this investigation consisted of the highly insoluble antifungal agent, griseofulvin,[1] with succinic acid as the carrier. The phase diagram for the binary system was prepared by the microthermal technique (4).

To determine any possible interaction between drug and carrier in aqueous solution, solubility studies were undertaken. An excess amount of drug was placed in 60-ml. test tubes equipped with screw caps and containing 30 ml. of an aqueous solution of the carrier in varying concentrations. The contents of each tube were equilibrated at 37° in a Gyrotory incubator shaker.[2]

At the end of this period, 1-ml. samples were withdrawn by means of a filter pipet. The griseo-

[1] Generously supplied by the Schering Corp., Bloomfield, N. J.
[2] Model G-25, New Brunswick Scientific Co., New Brunswick, N. J.