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Dissolution of Slightly Soluble Powders under Sink Conditions II: Griseofulvin Powders

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Abstract □ Dissolution studies were carried out on micronized and regular milled griseofulvin powders. A three-compartment dissolution apparatus previously developed by the authors was used. A barrier was used in the dissolution medium to prevent the floating masses from entering directly into the sink phase. The individual, wetted particles of these powders could pass through the barrier pores. It was demonstrated that these particles do not enter and dissolve in the sink phase due to the presence of the aqueous layer around them. The presence of a sink phase and the introduction of samples in the form of suspensions were considered necessary to obtain appropriate rank order in the dissolution rates. A modified Hixon and Crowell cube root law was applied to obtain dissolution-rate constants for two different particle-size griseofulvin powders.

Keyphrases □ Griseofulvin powders—dissolution □ Dissolution, griseofulvin powders—sink conditions □ Particle-size effect—griseofulvin dissolution □ UV spectrophotometry—analysis

The importance of dissolution studies as an index of drug availability from solid dosage forms is widely accepted. The need to maintain appropriate sink conditions to conduct suitable dissolution studies for slightly soluble drugs was mentioned in a previous paper (1). In drugs with very low solubility, the dissolution process is controlled by the interfacial rate constant. Since the interfacial rate constant is the same for each drug species, the reduction of particle size is the common approach to increase the drug availability from drug formulations. Several investigators (2–5) showed an increased absorption rate for griseofulvin when the particle size of the drug was reduced. Similar effects from particle-size reduction were noted for chloramphenicol (6) and various salts of tetracycline (7). The relationship between particle size and drug availability is well recognized and, as a result, several excellent review articles were published in the last 5 years (8–11).

The general problems (flocculation, flotation, agglomeration, and wetting) encountered in the *in vitro* dissolution-rate studies of slightly soluble powders under sink conditions were discussed in the first article (1) of this series. Although dissolution studies under sink conditions might be generally desirable, they are almost necessary for poorly soluble drugs to obtain meaningful results. Rapid saturation of the dissolution medium may not allow the visualization of even major formulation differences. The limitations of other available sink methods (12, 13) for dissolution studies of powders were mentioned earlier (1). Although the use of a diffusion cell (14) or a large volume of dissolution medium (15, 16) could be used to avoid concentration build up, a method that utilizes an organic sink phase might be of value in the dissolution studies.

The objectives of this investigation were to demonstrate the use of a previously developed dissolution apparatus (1) to conduct dissolution studies of a very poorly soluble compound, griseofulvin, and to show

an application of the modified Hixon and Crowell cube root law for such studies.

THEORY

Parrott *et al.* (17) modified the Hixon and Crowell cube root law (18) for a single spherical particle. Niebergall and Goyan (19) extended this law to apply it to a multiparticulate system. In its integrated form, the cube root law is

$$Wo^{1/3} - Wt^{1/3} = kt \qquad \text{(Eq. 1)}$$

where Wo is the initial weight of powder, Wt the weight of the undissolved powder at time t, and k is the rate constant. This cube root law has been derived on the basic assumption that the amount of the solute needed to saturate the dissolution medium is much greater than the solute concentration in the dissolution medium, $Cs>>>>Ct$; therefore, $Cs - Ct$ can be taken as constant. If dissolution of a very poorly soluble material is carried out under appropriate sink conditions, the concentration of such a drug in the dissolution medium would essentially remain constant. Under these conditions, the modified cube root law for a multiparticulate system could be applied. A plot of $Wt^{1/3}$ *versus* t should give a straight line with a slope of k. Given various samples of the same drug with different particle sizes, the number of drug particles and conversely the surface area would differ for the same weight of powder. This difference in surface area should result in a difference in the dissolution-rate constant, k. Such a rate constant could be used an an index of drug availability from such powders and as an aid in formulation development and control.

EXPERIMENTAL

Chemicals and Materials—Regular milled and micronized griseofulvin powders were used without further sizing.[1] The *n*-butyl acetate employed was reagent grade.[2] FD&C Orange No. 2,[3] isopropyl myristate,[4] and polysorbate 80[5] were also used.

Transport Studies of FD&C Orange No. 2—The dissolution apparatus described earlier (1) was used to conduct these studies. A 200-mesh screen was used as a barrier in the dissolution medium. In the preliminary studies on the dissolution of regular and micronized griseofulvin powders, it was observed that both forms of griseofulvin formed partial suspensions in the dissolution medium under the force of agitation. These fine particles in suspension were capable of passing through the 200-mesh screen barrier. It was, therefore, necessary to determine if hydrophobic particles that can pass through this barrier can dissolve directly in the organic sink phase.

A very fine[6] FD&C Orange No. 2 powder was selected for these experiments. This dye is insoluble in water even in the presence of polysorbate 80 (0.05%) and is quite soluble in isopropyl myristate (33.75 mg./ml. at 37°). Four propellers were attached to the stirrer located in Compartment A, as described in the previous communication (1). Six hundred milliliters of distilled water containing 0.05% polysorbate 80 which was previously equilibrated to 37° was placed below the barrier in Compartment A with the help of a long-stem separator. Seven hundred and eighty milliliters of isopropyl myristate was placed in Compartments B and C (two-compartment system). Stirrers for Compartments A and B, which were previously set at 100 and 150 r.p.m., respectively, were started and the system was allowed to equilibrate for 45 min. A suspension of 250.0 mg. of FD&C Orange No. 2 was made using 1.5 ml. of dissolution medium within the sample injector by stirring with a capillary tube. A Whatman No. 1 filter paper disk was used to cover the injector opening. This suspension was injected into the dissolution medium over a period of 30 sec. One-milliliter samples were removed from the organic phase at regular intervals, and the sample volume was replaced immediately with isopropyl myristate. The samples were diluted with isopropyl myristate and assayed spectrophotometrically at 482 nm., using a Beckman DU-2 spectrophotometer.

[1] Supplied by McNeil Laboratories, Inc.
[2] Fisher Scientific Co.
[3] Magnus, Mabee and Raynard, Inc.
[4] S. B. Penick and Co.
[5] Atlas Chemical Ind.
[6] Under microscopic examination, the average size of the individual particles was found to be under 1 μ.

Table I—Transport of FD&C Orange No. 2 from Suspension in Aqueous Phase to the Organic Phase Using 200-Mesh Screen at 100 r.p.m. and 37°

Hours	Weight[a] of Dye Dissolved in Organic Phase, mg.
0.5	2.3
1.0	3.1
2.0	4.8
3.0	6.0
4.0	7.1
5.0	7.7

[a] Each value is an average of two experiments.

Dissolution of Griseofulvin Powders under Nonsink Conditions—These experiments were carried out in Compartment A. Six hundred milliliters of distilled water containing 0.05% polysorbate 80 was used as the dissolution medium. A 250-mg. sample of griseofulvin was introduced into the dissolution medium either as a dry powder or as a suspension. About 1.5 ml. of dissolution medium was removed from the top of the screen while filtering through a 0.45-μ Acropor filter[7] using a Swinnex-13 filter unit. One milliliter of this filtrate was diluted with distilled water and assayed spectrophotometrically at 295 nm., using a Beckman DU-2 spectrophotometer. The remaining filtrate was returned to the dissolution medium, and 1.0 ml. of fresh dissolution medium was forced through the filter unit to flush back the griseofulvin that might have deposited on the back of the filter.

Dissolution of Griseofulvin Powders under Sink Conditions—These experiments were carried out as described under transport of FD&C Orange No. 2, except that the organic phase used was *n*-butyl acetate. The samples were introduced either as dry powder or as a suspension. A glass cover was used to prevent evaporation of the organic phase. Samples from the aqueous phase were withdrawn from the top of the screen as described under nonsink conditions by introducing the needle through the organic phase while injecting air, filtering the sample, diluting with distilled water, and assaying as described earlier. Samples from the organic phase were removed, diluted with methanol, and assayed spectrophotometrically at 290 nm., using a Beckman DU-2 spectrophotometer. A volume of each phase equal to the sample volume was replaced immediately with appropriate solvent. The volume of the aqueous phase removed was replaced while backflushing the filtration unit.

RESULTS AND DISCUSSION

Transport of FD&C Orange No. 2 from Aqueous Suspension to Organic Phase—In transport studies on FD&C Orange No. 2, it was observed that the dye particles moved across the screen barrier immediately after the introduction of the sample. The data in Table I show that even after 5 hr., only 3.1% of the dye dissolved in the organic phase. This surprisingly low concentration in the organic phase is probably due to the fact that most of the dye particles are completely wetted in the aqueous phase, and there is a thin aqueous layer around the dispersed dye particles. These wetted particles cannot come in contact with the organic phase and therefore are not dissolved in it.

A comparison of the solubilities of FD&C Orange No. 2 in the isopropyl myristate (33.75 mg./ml. at 37°) and that of griseofulvin in *n*-butyl acetate (6.3 mg./ml. at 37°) shows that the dye has a greater solubility in its sink phase than does griseofulvin. Since there is a direct relationship between the solubility of a compound and its dissolution rate (17), there would be less tendency for griseofulvin to dissolve directly in the organic phase than for the FD&C Orange No. 2 dye.

Since griseofulvin has some solubility in the dissolution medium (18.4 mg./l. at 37°),[8] there is a greater probability for the griseofulvin

[7] The Acropor filters are reinforced with nylon cloth and can allow a two-way filtration without rupture.
[8] Solubility in dissolution medium saturated with *n*-butyl acetate is 54.0 mg./l. at 37°.

Table II—Dissolution of Micronized and Regular Griseofulvin Powders under Nonsink Conditions Using Samples as Dry Powders and Suspensions at 100 r.p.m. and 37°

Dissolution Time, min.	Weight[a] of Griseofulvin in Solution, mg.			
	Dry Powder Samples		Suspension Samples	
	Micronized	Regular	Micronized	Regular
5	8.80	8.40	10.06	10.06
10	10.03	10.05	10.07	10.06
20	10.06	10.04	10.06	10.07
30	10.06	10.06	10.06	10.07
40	10.07	10.06	10.07	10.06
60	10.06	10.06	10.06	10.06

[a] Each value is an average of two experiments.

particles to be wetted and therefore less chance for the particles that pass through the barrier to dissolve directly in the organic phase. Because of these arguments, it is felt that when dissolution studies are conducted with griseofulvin under sink conditions, using samples as dry powders or suspensions, the error involved in the dissolution data due to the direct contact of griseofulvin particles with the organic phase would be insignificant.

The experiments with the dye show that particles in suspension do not behave in the same manner as floating masses of powders. In the case of floating masses, the particles are not completely wetted; in the absence of some barrier in the dissolution medium, these masses enter the organic phase and dissolve directly in that phase. Wetted particles in suspension, even if they pass through the barrier pores, still do not dissolve in the organic phase and probably will not be a problem in dissolution studies.

The dye studies could also explain why dissolution of a drug in the gastrointestinal contents is necessary before any absorption can take place. Due to the presence of physiologic surfactant in the gastrointestinal contents (20–22) and its motility, the drug would be expected to be wetted rapidly. The wetted particles would be in contact with the gastrointestinal membranes through the wetting aqueous layer around the particles. Thus, in spite of the very fine particle size of the drug or its great solubility for the lipoid membrane, the drug would not dissolve directly into the lipoid membrane.

Dissolution of Griseofulvin Powders under Nonsink Conditions—The dissolution studies of micronized and regular griseofulvin powders under nonsink conditions (Table II) show that a rank order in the dissolution rates of the two powders was not determinable under these conditions when the samples were introduced as dry powders or as suspensions. This failure was probably due to rapid saturation of the dissolution medium in the absence of appropriate sink conditions. The data show that when dry powder samples are used, there is less dissolution in the beginning for regular powder than for the micronized powder; however, the difference is very small and probably not significant. In the case of samples introduced as suspensions, there seems to be rapid saturation of the dissolution medium for both powders, and no noticeable difference in the dissolution rates of these powders could be detected.

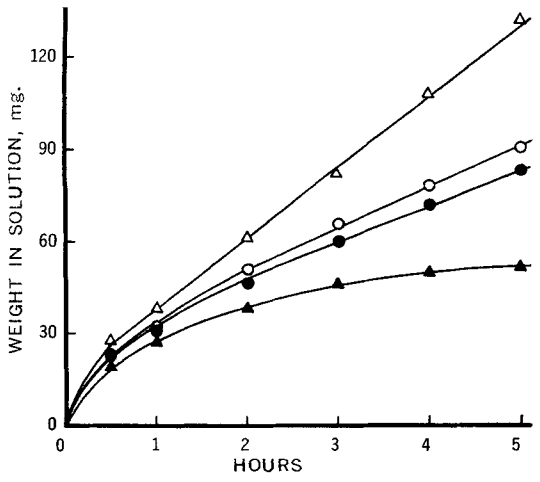

Figure 1—*Dissolution profiles of micronized and regular griseofulvin powders under sink conditions, using samples as dry powders and suspensions at 100 r.p.m. and 37°. Key: △, micronized suspension; ○, regular suspension; ●, regular dry powder; and ▲, micronized dry powder.*

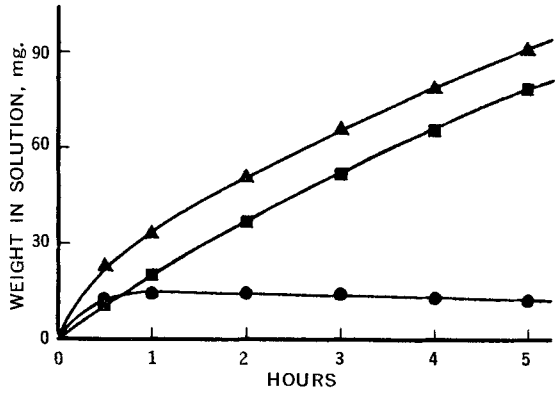

Figure 2—*Dissolution and partitioning of regular milled griseofulvin powder. Key: ●, concentration in dissolution medium; ■, concentration in n-butyl acetate; and ▲, cumulative dissolution.*

Dissolution of Griseofulvin Powders under Sink Conditions—The dissolution profiles of micronized and regular griseofulvin powders introduced as dry powders and suspensions are shown in Fig. 1. These studies show that when the griseofulvin samples were introduced as dry powders, there was a higher dissolution rate for regular griseofulvin compared to the micronized form. These results are in contrast with *in vivo* findings (2–5). This discrepancy is probably due to the micronized powder being in the form of glomerates because of the presence of greater static charge and higher surface energies. The regular powder was almost free of glomerates. When both powders were introduced into the dissolution medium as dry powders, a major portion of the regular powder was able to break up into individual particles, whereas even the presence of the lower impeller did not break up the glomerates of the micronized powder. These glomerates settled at the bottom of the dissolution vessel, giving a lower effective surface area and, therefore, a lower dissolution rate than with the regular powder.

Dissolution profiles for griseofulvin powders, when the samples were introduced in the form of a suspension (Fig. 1), show a good rank order for the two particle-size powders. Dissolution and partitioning profiles are shown in Figs. 2 and 3. These figures show almost constant concentration of griseofulvin in the dissolution medium. Under these conditions, the cumulative dissolution profiles should follow the modified Hixon and Crowell cube root law (19).

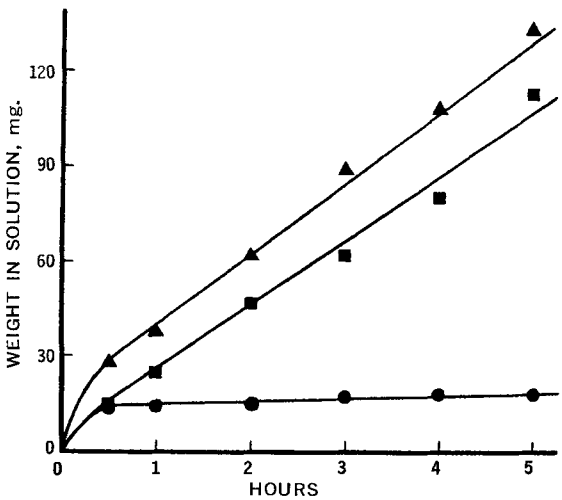

Figure 3—*Dissolution and partitioning of micronized griseofulvin powder. Key: ●, concentration in dissolution medium; ■, concentration in n-butyl acetate; and ▲, cumulative dissolution.*

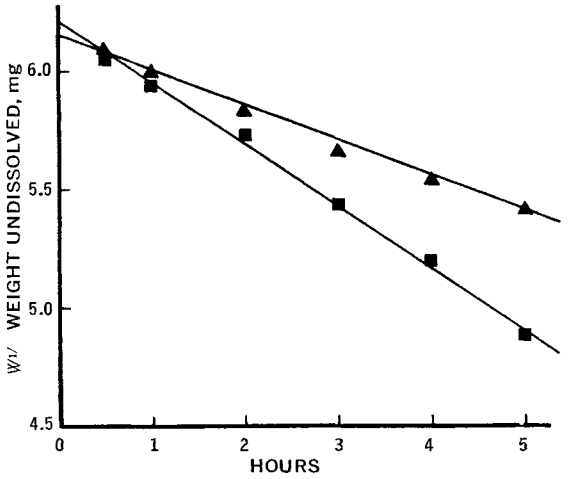

Figure 4—*Plots of* $Wt^{1/3}$ versus *time. Key:* ▲, *regular milled griseofulvin powder; and* ■, *micronized griseofulvin powder.*

Figure 4 shows good straight-line plots for the dissolution of griseofulvin powders under sink conditions when the samples were introduced in the form of suspensions. The ratio of k values is 0.56. The authors did not conduct any *in vivo* studies for these powders. Other investigators have, however, reported that the micronized griseofulvin is twice as well absorbed as the regular milled powder (2). The ratio of rate constant from present studies is in general agreement with these *in vivo* studies. This was possible due to two factors. First, while making the suspensions, the glomerates were broken up and both sized powders were readily dispersed in the dissolution medium, thus making relative surface areas available for dissolution. Second, there was no saturation of the dissolution medium due to the presence of sink conditions.

In the present studies, a 200-mesh screen was used as a barrier in the dissolution medium. Although the wetted particles of the powders under study could pass through the barrier pores, the barrier was needed to prevent the direct dissolution of the powders in the sink phase. Preliminary studies without this screen barrier showed that the powders could enter directly into the organic phase when introduced as dry powders or wetted suspensions. This was due to the entrapment of air in glomerates in the case of dry powders and to a slight foam formation while making suspensions of the samples. The use of a screen barrier for suspension samples was also needed to keep the geometry of the dissolution system the same throughout the study.

These studies demonstrate a successful use of the previously developed apparatus (1) for dissolution studies of very sparingly soluble fine powders under sink conditions. The studies show a need for sink conditions to differentiate the dissolution patterns of different powders such as griseofulvin. These studies also demonstrate a technique to overcome the problems due to excessive agglomeration in the dissolution of such fine powders. In general, a rate constant would more fully describe the dissolution process than do dissolution profiles or some points on the profile (such as t_{30} or t_{50}). Dissolution profiles can only give a qualitative rank order but not a single quantitative value which could be used for correlation with *in vivo* data. Single points on the dissolution profile would not describe the dissolution behavior on either side of such points. Although a dissolution rate constant is often difficult to obtain for such multiparticulate systems, these studies show that such a rate constant is possible to obtain for such powders when studies are conducted under appropriate sink conditions. The rate constant obtained in these studies using the modified Hixon and Crowell cube root law (19) might be a useful parameter for comparing the dissolution characteristics of the powders. The apparatus developed by the authors (1) allows a great flexibility and versatility for such studies.

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