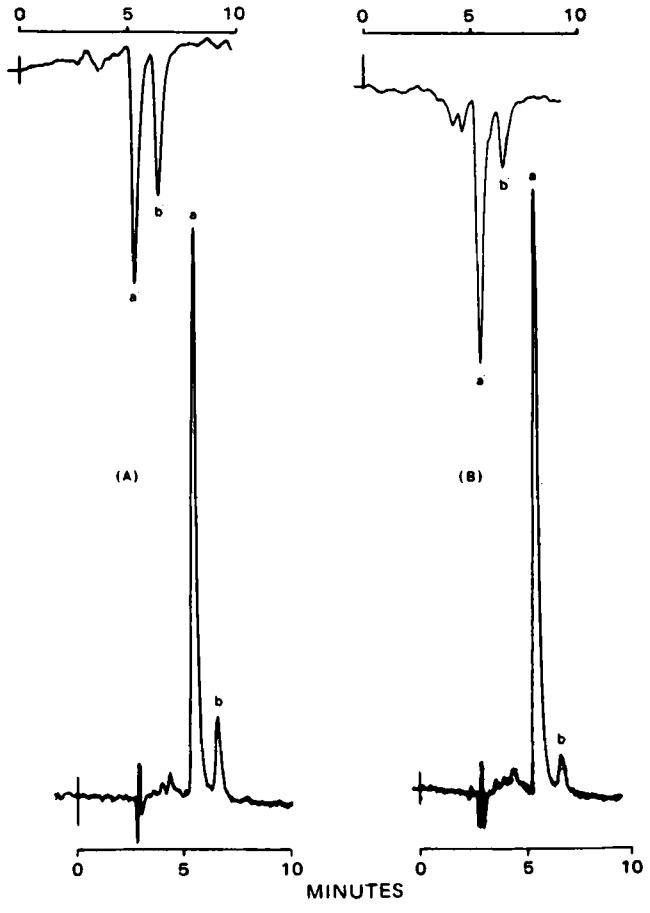

Figure 1—*Chromatograms of human urinary griseofulvin metabolites. Key: A, untreated sample; and B, the same sample after incubation overnight with β-glucuronidase at 37°. Peak response in A represents the original urine concentration; in B, the urine concentration was diluted to one-half. The top and bottom chromatograms were obtained with fluorescence and UV detection, respectively.*

detectors is that the purity of a separated component in a chromatogram may be evaluated with the peak response ratio of the two detections; if the peak response ratio of a component is different from that of the standard, then either the peak response represents a different species or some impurities may have eluted with the same retention time.

Peaks a and b, which were not observed in the blank urine sample, had retention times identical to those of standards of 6-desmethylgriseofulvin and griseofulvic acid, respectively. Furthermore, the UV–fluorescence peak response ratios of peaks a and b also were the same with respect to their standards. It is concluded that peak a represents 6-desmethylgriseofulvin and that peak b represents griseofulvic acid. The presence of griseofulvic acid in urine samples was evidenced further in TLC studies. With a silica gel plate[2] and chloroform–methanol (10:1 v/v), two urinary metabolites were observed and identified by comparison with 6-desmethylgriseofulvin (R_f 0.18) and griseofulvic acid (R_f 0.05) standards. 4-Desmethylgriseofulvin (R_f 0.36) was not found in the urine samples.

The 6-desmethylgriseofulvin standard was isolated from dog urine according to a literature method (3). The purified product was positively identified as 6-desmethylgriseofulvin by a melting-point measurement (4) and by its mass spectrum, which was identical with that reported previously (5). The griseofulvic acid standard was synthesized by reacting griseofulvin with boron tribromide at −60°. The purified product showed a melting point and a mass spectrum identical to those reported for griseofulvic acid (4, 5). The 4-desmethylgriseofulvin standard was prepared according to a literature method (4), and it also was identified by its melting point and its mass spectrum.

The griseofulvic acid formation is speculated to occur *via* microsomal demethylation at the 2′-position and subsequent tautomerization of the 2′-enol to the 2′,4′-dione. The pharmacokinetics of this metabolite and its toxicological effect are under investigation.

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Effect of Instrumental Vibration Levels on Dissolution

Keyphrases □ Dissolution tests—effects of instrumental vibration, tablets □ Vibration—effect on dissolution tests, tablets

To the Editor:

In the process of investigating the dissolution of two commercial enteric-coated aspirin tablets, large variations in dissolution profiles were observed between two dissolution apparatus (1). The dissolution profiles were followed in simulated intestinal juice for 10 hr using the dissolution procedure described in USP XIX (2). The apparatus[1], designated left (L) and right (R), were operated at a stirring speed of 50 ± 1.5 rpm throughout the study. The tablets in the L apparatus dissolved more slowly, leaving partial tablet residues after 10 hr of dissolution. Additionally, the dissolution profiles were low, indicating poor dissolution characteristics. However, in the R apparatus, tablets from the same batch dissolved completely in the same time period, and dissolution profiles were substan-

[2] Silica gel 60F, 0.05 mm thick, E. Merck, Darmstadt, West Germany.

[1] Hanson Research Corp., Northridge, Calif.

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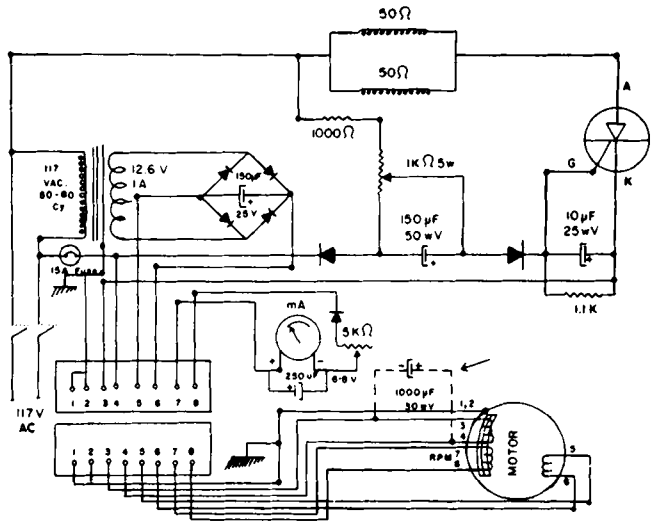

Figure 1—*Dissolution motor control circuit. Modification is indicated by arrow.*

tially higher at all times.

Upon observation, the L motor was noticed to sound and feel rough. Vibrations appeared to be the cause of the performance differences. Since both dissolution vessels were immersed in the same water bath and shared stands with the dissolution and stirring motors, vibrations could be transmitted by the motors *via* the shared stands. These vibrations might increase the extent of dissolution. To test this hypothesis, the mixers[2] and the dissolution motors were isolated from each other and from other components of the apparatus; supporting stands were sandbagged to reduce vibrations. Additionally, the shafts connecting the baskets to the dissolution motors were shortened to reduce shaft whip.

After these measures were taken, the dissolution profiles improved in likeness but continued to be high for the R apparatus. This difference in dissolution profiles could not be explained by random error for a given batch of tablets. When the dissolution motors were switched, the results interchanged. An analysis of variance (ANOVA) showed

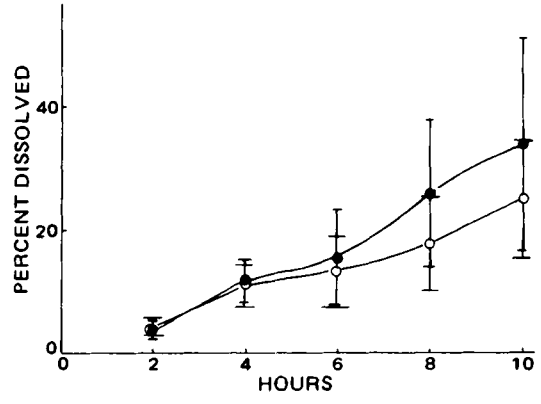

Figure 2—*Dissolution profiles of L apparatus. Key: ●, average of three observations before modification to rectifying circuit; and ○, average of five observations after modification to rectifying circuit. Vertical bars indicate ±1 SE around the mean.*

[2] Lightnin mixers, Mixing Equipment Co., Rochester, N.Y.

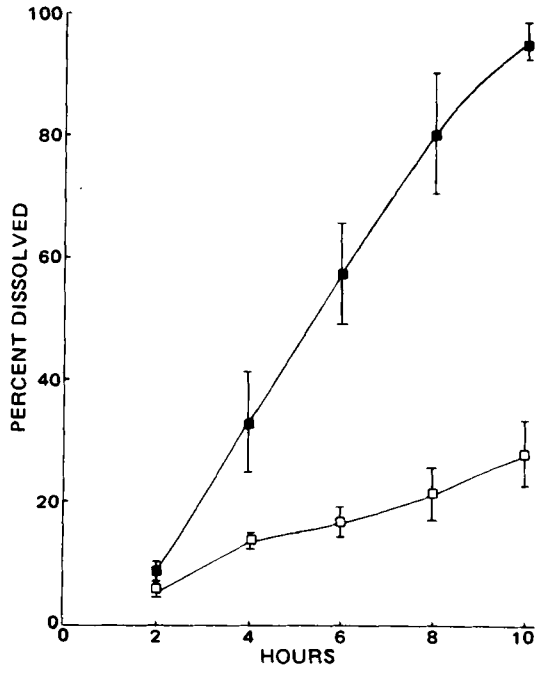

Figure 3—*Dissolution profiles of R apparatus. Key: ■, average of three observations before modification to rectifying circuit; and □, average of five observations after modification to rectifying circuit. Vertical bars indicate ±1 SE around the mean.*

that dissolution profiles for a given batch were still significantly different at the $p = 0.03$ level, indicating that the dissolution apparatus were not operating in a matched fashion. Further reduction of vibration levels was necessary. These observations are in agreement with those of Beyer and Smith (3), but differ in that Beyer and Smith indicated their sources of vibration to be external in nature, such as the circulating pump and activities in the surrounding environment, originating from various benchtop sources.

The speed control circuit appeared to require a 1000-μF capacitor to absorb the high-frequency component of the applied pulses and to smooth out the jerky movement of the motor. This modification can be observed in Fig. 1; connections of the capacitor are designated as dotted lines. Subsequently, the dissolution profiles from the same batch appeared to be more evenly matched. Hence, unlike earlier reports (3), the vibrations we observed seem to have their origins within the motor. An analysis of variance after the electrical modification determined that the adjustment to the circuit decreased vibration levels for each apparatus such that the difference between the two was no longer statistically significant. While the L apparatus dissolution profile did not change very much (Fig. 2), the R apparatus had a large reduction in vibration levels, resulting in a significant reduction in the dissolution profile at all times. By making the modification to the speed control circuit, we were able to reduce the dissolution profile of the R apparatus by 20–70% in 2–10 hr (Fig. 3).

Because the capacitor used in the modification did not affect both instruments equally, there may be an inherent difference between the two dissolution motors. The addition of the capacitor treated the symptom but did not cure the problem. Even though a better speed control circuit may have resulted in even lower vibration levels,

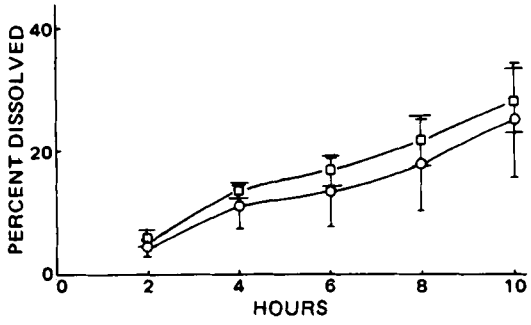

Figure 4—*Dissolution profiles of both dissolution apparatus after modification, indicating matched behavior. Key:* ○, *average of five observations for L apparatus; and* □, *average of five observations for R apparatus. Vertical bars indicate* ±*1* SE *around the mean.*

the problem appears to lie within the motor. Such factors as the number of poles on the motor, the quality of the brushes and the bearings, and the internal lubrication play an important role. While the performances of the two apparatus appeared to be matched statistically, the profiles obtained from the R apparatus were consistently higher than the L apparatus. This trend was observed throughout 200 dissolutions. The two dissolution apparatus now appeared to be matched, as seen by the similarity between the dissolution profiles obtained. The overall effect on the reduction in vibrations is summarized in Fig. 4.

Wagner *et al.* (4) indicated that high stirring speeds, such as the 200 rpm used for aminosalicylic acid tablets, tended to cause the tablets to disintegrate and dissolve with ease, masking the individual differences between tablets. At stirring speeds approximating 50 rpm, these individual characteristics were discernible in the differing tablet dissolution profiles. At these lower speeds, vibration levels begin to play a more important role and may cause a decrease in the dissolution time, suggesting good performance for poorly dissolving tablets. The apparatus differences due to vibration levels may not be detected in tablets that dissolve rapidly because the time for vibrations to have a significant effect may not exist and the vibrational component of the motor also may be reduced at higher speeds.

If we assume that vibrations are at a constant level and cause an increase in the true revolutions per minute, at high speeds the percent change will be small and may be unnoticed. However, with dosage forms that dissolve slowly due to design or to poor solubility of the active ingredient, the effect of these vibrations may be more obvious. Standardization in vibration levels should be achieved to operate dissolution equipment in a matched fashion. To determine whether dissolution equipment are mismatched, dissolutions using the same "standard" batch of tablets should be run on both apparatus and the results compared statistically. Vibrational levels in the dissolution apparatus may be partly responsible for differences in dissolution data observed between laboratories.

We suggest that the USP indicate the source and quality of the dissolution motor and the electronic equipment necessary for its control. Other parameters such as the distance from the dissolution motor to the stand supporting it and the distance from the rotating basket to the point connecting the shaft to the dissolution motor should be specified; all of these factors yield potentially different results with different levels of vibration dampening resulting in different stirring speeds.

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