New Method of Solid-State Dispersion for Increasing Dissolution Rates

Sir:

The authors have recently reported on the potential value of solid-state dispersion, *viz.*, solid solutions, in enhancing the dissolution rate and gastrointestinal absorption of drugs (1–4). Although this approach has been quite successful in modifying the dissolution characteristics of griseofulvin (3) and chloramphenicol (4), the application of solid solutions formed by fusion technique, for enhancing dissolution, is somewhat limited. The method has been found inapplicable to a number of drugs which are unstable at or near their melting points, or which fail to crystallize from the mixed melt.

Therefore, other methods have been sought to obtain solid-state dispersions of insoluble drugs in water-soluble matrices. In 1965, Tachibana and Nakamura (5) reported a method for preparing aqueous dispersions of β-carotene by using water-soluble polymers.

An earlier report by Stone (6) described a similar technique for the preparation of water dispersible antibiotics. This preliminary communication concerns the use of the dispersion method to obtain physically modified forms of a drug, which are much more rapidly soluble than the pure compound. Although the mechanism of the dispersion has not yet been rigorously established, the striking findings and the apparent general applicability of the method warrant consideration.

The authors' initial studies were concerned with dispersions of griseofulvin in polyvinylpyrrolidone (PVP). The drug was crystallized from a 1% solution in chloroform containing 0, 5, 10, and 20% PVP. In each case the solvent was evaporated at 37° until a clear film, essentially free of solvent, remained. The film was further dried to constant weight, and the material was then sized using a Syntron shaker. The 40–50 mesh particles were collected for dissolution rate studies.

Sekiguchi *et al.* (7) have reported that griseofulvin forms a 1:1 solvate with chloroform. In the present work, the existence of the solvate was confirmed; but it was found to be quite unstable and decomposed rapidly under our drying condition. In order to determine the dissolution rate of the solvate, a sample was carefully prepared. Analysis of the material immediately before dissolution rate studies indicated that it contained about 23% chloroform corresponding to a 1:1 solvate.

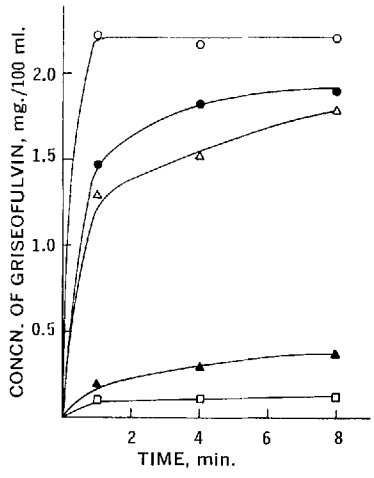

Fig. 1.—Dissolution rate of micronized griseofulvin (▲); griseofulvin chloroformate (□); griseofulvin–PVP, 1:5 (△); griseofulvin–PVP, 1:10 (●); and griseofulvin–PVP, 1:20 (○).

TABLE I.—DISSOLUTION STUDIES OF GRISEOFULVIN

Sample	Relative Dissolution Rate 1 min.	4 min.
Micronized griseofulvin	1.0	1.0
Griseofulvin–chloroform solvate	0.5	0.4
Griseofulvin–PVP (1:5)	6.1	5.1
Griseofulvin–PVP (1:10)	7.2	6.1
Griseofulvin–PVP (1:20)	11.0	7.3

Particulate dissolution rate was determined in the following manner. Each sample, containing 10 mg. of griseofulvin, was added to a 600-ml. beaker containing 300 ml. of distilled water at 37°. Stirring was provided by an overhead stirrer operating at 150 r.p.m. In order to overcome the "nonwetting" character of the micronized griseofulvin[1] (included in the study to provide a basis of comparison) the dissolution medium contained 0.02% polysorbate 80. The wetting agent was used in each dissolution study, although it proved inconsequential with the PVP–griseofulvin samples. After the addition of the drug, 5-ml. samples of the dissolution medium were taken periodically, rapidly filtered through a Millipore filter (0.45 μ), and assayed for griseofulvin using a Beckman DB recording spectrophotometer.

The results of this investigation are shown in Fig. 1. Table I provides a comparison of the dis-

[1] The griseofulvin used in this investigation was generously supplied by the Schering Corp.

solution rate of the various samples with the dissolution rate of micronized griseofulvin. The solid-state dispersion of griseofulvin in PVP results in a five- to tenfold increase in the dissolution rate of the drug. In the absence of wetting agent in the dissolution medium the enhancement is still greater.

Although some complexation seems to exist between griseofulvin and PVP (on the basis of preliminary solubility studies), the authors do not believe that this imposes a restriction on the utility of this dispersion technique for a large number of water-insoluble drugs. Based on our initial observations, it is suggested that griseofulvin is dispersed molecularly in the polymer film and forms a solid solution with PVP in the film. It is believed that this approach to the modification of drug properties may be of broad import in the area of biopharmaceutics and may find significant therapeutic application.

(1) Goldberg, A. H., Gibaldi, M., and Kanig, J. L., *J. Pharm. Sci.*, **54**, 1145(1965).
(2) *Ibid.*, **55**, 482(1966).
(3) *Ibid.*, **55**, 487(1966).
(4) Goldberg, A. H., Gibaldi, M., Kanig, J. L., and Mayersohn, M., *ibid.*, **55**, 581(1966).
(5) Tachibana, T., and Nakamura, A., *Kolloid-Z. Polymere*, **203**, 130(1965).
(6) Stone, I. M., U. S. pat. 3,089,818 (1963).
(7) Sekiguchi, K., Ito, K., Owada, E., and Ueno, K., *Chem. Pharm. Bull. (Tokyo)*, **12**, 1192(1964).

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Received July 25, 1966.
Accepted for publication August 15, 1966.

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Books

REVIEW

Drug Identification. Edited by C. A. JOHNSON and A. D. THORNTON-JONES. The Pharmaceutical Press, 17 Bloomsbury Square, London, W. C. 1, England, 1966. ix + 133 pp. 14 × 22 cm. Price $4.90.

This book subtitled "a scheme for the identification of organic chemicals used in medicine and pharmacy" is an extension of the techniques first introduced in 1904 by Mulliken in his publication *The Identification of Pure Organic Compounds.* Within the past twenty-five years, numerous investigators have authored reference works based on accumulated data for characterization analysis. In general, a compound is subjected to preliminary tests including solubility in selected solvents, reaction with acidic and basic solutions, melting point, etc., as well as an elemental analysis. Additional tests may be performed to identify functional groups present in the compound. Based on the assigned presence of C, H, O, N, S, F, Br, Cl, I, and metals in the test sample, the analyst refers to tables which subdivide the book into combinations of elements as they frequently occur in drug substances. Compounds listed in each table are arranged in order of increasing boiling or melting points. The schematic approach ends here, and the individual is confronted with final identification by conducting the tests (e.g. colorimetric, precipitation, light-absorption, preparation, or derivatives, etc.) included for compounds which fit the general information obtained to this point.

The data contained in this volume are a creditable compilation but should be augmented for extensive and accurate identification. Improvement, is required in the form of definitive identification tests for many substances, and wherever feasible the tables should be expanded to include entries for nonofficial drugs. A worthwhile addition would be classical tabulations by functional groups which could be used in conjunction with accrued preliminary data for rapid identification of many compounds.

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NOTICES

Methods of Biochemical Analysis. Vol. 14. Edited by DAVID GLICK. Interscience Publishers, a div. of John Wiley & Sons, 605 Third Ave., New York, N. Y. 10016, 1966. vii + 562 pp. 15.5 × 23.5 cm. Price $15.

Biochemical Preparations. Vol. 11. Editor-in-Chief ANDREAS C. MAEHLY. John Wiley & Sons, Inc., 605 Third Ave., New York, N. Y. 10016, 1966. xii + 147 pp. 15 × 23 cm. Price $8.

Optical Page Reading Devices. By ROBERT A. WILSON. Reinhold Publishing Corp., 430 Park Ave., New York, N. Y. 10022, 1966. ix + 197 pp. 15.5 × 23.5 cm. Price $10.

The Amphetamines: Toxicity and Dependence. By ORIANA JOSSEAU KALANT. Charles C Thomas, 301–327 E. Lawrence Ave., Springfield, Ill., 1966. xii + 151 pp. 15.5 × 23.5 cm. Price $6.75.