Correlation of Pharmacologic Activity and Dissolution Rates of Reserpine-Desoxycholic Acid Dispersions

Sir:

The usefulness of solid-state dispersions for enhancing the dissolution rate of drugs has been demonstrated in a number of recent reports (1–5). The principal reason for the observed effects appears to be particle size reduction. An interesting example of the enhanced pharmacologic activity of such dispersions has been provided by Malone *et al.* (6). These workers found a significant increase in the blepharoptotic activity of reserpine in mice after oral administration of the drug as a solid dispersion in desoxycholic acid (DCA). A correlation between the composition of the reserpine-DCA dispersion and apparent biologic activity was also noted in that an increase in the DCA:reserpine ratio resulted in an increase in activity (see Table I). Results of studies to be reported in this communication suggest that particle size reduction of reserpine in the dispersion, leading to increased dissolution and absorption rate, and possibly increased availability of reserpine, is likely to be a major factor in the enhancement of pharmacologic activity.

Reserpine[1] and DCA[2] dispersions were prepared according to the methods of Malone *et al.* (6) which involve co-precipitation of the materials from chloroform–absolute alcohol solutions upon evaporation of the solvent system. Attempts to determine the dissolution rate of reserpine in aqueous systems were unsuccessful because of assay difficulties and adsorption problems introduced by the extremely low aqueous solubility of the drug. Hence, dissolution rates of reserpine from 12 to 20-mesh particles of the various preparations were determined in the following manner. Each sample, containing an equivalent of 150 mg. reserpine, was added to a round-bottom flask containing 300 ml. of ethyl acetate (certified A.C.S. grade) at 37° ± 0.1°. Stirring was provided by means of an overhead motor, connected to a Teflon blade, operating at 50 r.p.m. Samples were withdrawn at periodic intervals, filtered, diluted 1:10 with methanol, and assayed for reserpine using a Beckman DB-G spectrophotometer at 268 mμ. Desoxycholic acid appeared to be essentially "insoluble" in ethyl acetate. Solutions of DCS equilibrated in ethyl acetate at room temperature and 37°, upon 1:10 dilution, showed no spectral activity from 350 mμ to 220 mμ. In addition, the spectrum of reserpine at various concentrations was found to be identical in ethyl acetate and ethyl acetate saturated with DCA.

The dissolution data plotted in Fig. 1 indicate an increased dissolution rate of reserpine from the DCA dispersions. The greater the percentage of DCA in the dispersion, the faster the dissolution of reserpine. The raw dissolution data were replotted assuming that dissolution followed an apparent first-order process under nonsink conditions, as previously discussed by Gibaldi and Feldman (7). These plots are shown in Fig. 2.

TABLE I—CORRELATION OF DISSOLUTION DATA AND BIOLOGIC ACTIVITY OF VARIOUS RESERPINE-DCA DISPERSIONS

Molar Composition of Dispersions (Reserpine: DCA)	$k \times 10^4$ (mg.$^{-1}$min.$^{-1}$)	Ratio of Rate Constants	Oral Potency[a]
1:0	2.55	—	—
1:4	3.68	1.4	2.6
1:8	5.38	2.1	2.8
1:16	8.10	3.2	3.8
1:32	16.3	6.4	1.9

[a] Peak blepharoptotic activity after oral administration, as compared to the peak activity of reserpine base after oral administration (from *Reference 6*).

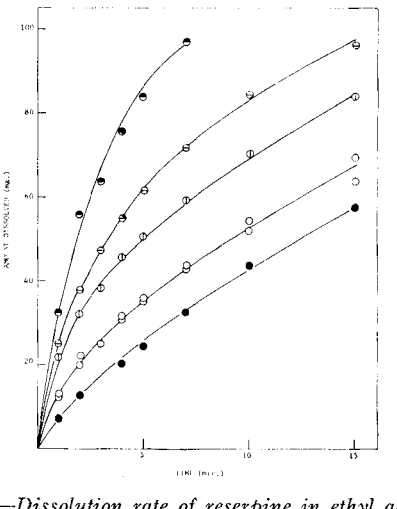

Fig. 1—Dissolution rate of reserpine in ethyl acetate from various preparations. Key: ●, reserpine-DCA, 1:0; ○, 1:4; ◑, 1:8; ⊖, 1:16; ◓, 1:32.

[1] Generously supplied by Ciba Pharmaceutical Company.
[2] Special enzyme grade, Mann Research Laboratories, Inc.

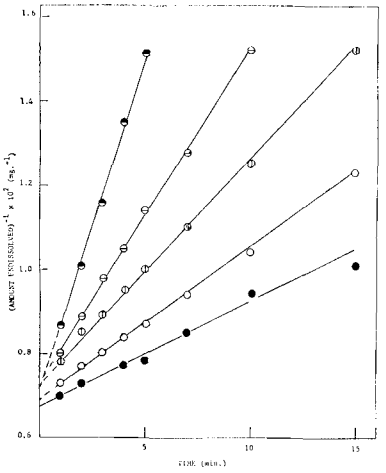

Fig. 2—Second-order plot of reserpine dissolution data assuming dissolution was apparent first order under nonsink conditions. Key: ●, reserpine–DCA, 1:0; ○, 1:4; ◑ 1:8; ⊖, 1:16; ◓, 1:32.

The apparent second-order rate constants were calculated and these are reported in Table I together with the corresponding ratios. A rank correlation is noted between the apparent second-order dissolution rate constants and the biologic activities of the various reserpine preparations. The sole exception is the 1:32 reserpine–DCA dispersion which is significantly less biologically active than would be predicted by the dissolution data.

The use of organic solvents in correlation studies between *in vitro* and *in vivo* data is rarely desirable or logical. However, as noted by Levy (8) dissolution in organic solvents does reflect adequately the particle size of the drug. Furthermore, dissolution in an organic solvent may reflect changes in crystal structure. To explore the latter possibility, diffraction spectra were obtained for reserpine and DCA, separately precipitated from the solvent system, and for various dispersions, using a General Electric XRD-6 diffractometer.[3] All samples appeared to be noncrystalline. In view of the absence of solution interaction between DCA and reserpine in ethyl acetate, and the lack of change in crystal form, it is concluded that the physical state of reserpine (*i.e.*, an extremely fine particle size attained by co-precipitation with DCA) is responsible for the increased dissolution rates observed with the reserpine-DCA dispersions.

(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) Mayersohn, M., and Gibaldi, M., *ibid.*, **55**, 1323 (1966).
(6) Malone, M., Hochman, H. I., and Nieforth, K. A., *ibid.*, **55**, 972(1966).
(7) Gibaldi, M., and Feldman, S., *ibid.*, **56**, 1238(1967).
(8) Levy, G., paper presented to the Industrial Pharmacy Section, APhA Academy of Pharmaceutical Sciences, Dallas meeting, April 1966.

MILO GIBALDI
STUART FELDMAN
THEODORE R. BATES*

Department of Pharmaceutics
School of Pharmacy
State University of New York at Buffalo
Buffalo, NY 14214

Received January 2, 1968.
Accepted for publication February 9, 1968.
*Present address: Pharmaceutics Department, Pharmacy Research Institute, University of Connecticut, Storrs, CT 06268

[3] The authors thank Dr. Eli Shefter for providing the diffraction data.

Keyphrases

Reserpine–desoxycholic acid dispersions—solid state
Solid state dispersions—pharmacologic activity effect
Dissolution rate–reserpine–desoxycholic acid dispersion

Antidepressive Effect of N-3,4,5-Trimethoxybenzoyl Heptamethylenimine

Sir:

It was Luts *et al.* (1) who reported on the synthesis and preliminary pharmacological investigation of *N*-3,4,5-trimethoxybenzoyl heptamethylenimine. As stated by these authors, unlike other amines containing trimethoxybenzoyl group the compound is void of depressant and analgesic action; moreover, it exerts a mild stimulating effect.

In a series of studies concerned with a large number of derivatives of heptamethylenimine substituted by benzoic acid the above-mentioned compound has also been synthesized and subjected to close pharmacological investigation.

Synthesis was carried out principally by the method reported by Luts *et al.* (1).