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Y. FULMER SHEALY▲
JOE D. CLAYTON
Kettering-Meyer Laboratories
Southern Research Institute
Birmingham, AL 35205

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▲ To whom inquiries should be directed.

Failure of USP Tablet Disintegration Test to Predict Performance in Man

Keyphrases ☐ Aminosalicylic acid enteric-coated tablets—results of compendial disintegration testing compared to plasma levels in man ☐ Plasma levels, aminosalicylic acid and metabolites—after administration of enteric-coated tablets, compared to dissolution data ☐ Tablet disintegration, compendial method—results for enteric-coated aminosalicylic acid tablets compared to plasma levels in man ☐ Excretion, fecal—enteric-coated aminosalicylic acid tablets, man

Sir:

An enteric-coated tablet of aminosalicylic acid[1], purchased on the open market in the United States by the Food and Drug Administration (FDA), was shown to pass all USP specifications in the FDA laboratories. In a four-way crossover study in eight normal adult volunteers, single oral doses of either 1 g. of aminosalicylic acid or the equivalent of 1 g. of the acid were administered as the enteric-coated tablet[1], a compressed tablet of aminosalicylic acid, a suspension of aminosalicylic acid in water, and a solution of the sodium aminosalicylate in water.

Blood samples were taken at 0, 0.33, 0.67, 1, 2, 3, 4, 6, 8, 12, and 24 hr. postadministration of each dose. The plasma samples, derived from the blood, were assayed for both aminosalicylic acid and its metabolite, *N*-acetyl-*p*-aminosalicylic acid, by a new specific analytical method (1). Plasma samples of all eight subjects at each sampling time assayed "zero" for both drug and metabolite following oral administration of the enteric-coated tablet. The assay sensitivity level was 0.5 mcg./ml. The average peak plasma levels of unchanged drug were 43.5, 16.7, and 8.86 mcg./ml. following oral administration of the solution, the suspension, and the compressed tablet, respectively. Drug levels were measurable over 6–8 hr. following the latter three dosage forms. The average peak plasma levels of the metabolite were 11.6, 12.3, and 10.9 mcg./ml. following the solution, the suspension, and the compressed tablet, respectively. Metabolite levels were measurable over 6–8 hr. following these dosage forms. Detailed results of this study will be published.

Since we did not know about the zero plasma levels of unchanged drug and metabolite in every subject following the enteric-coated tablet until all assays were completed, we never thought to ask the subjects to check their stools for intact tablets or large fragments of tablets. After the results were known, however, one of the eight subjects volunteered to take two more of the enteric-coated tablets. One tablet was excreted in his feces essentially intact (but with a small "hole" in one face) about 30 hr. postingestion. The other tablet did break up, but large pieces were excreted in the same feces. Figure 1 is a photograph showing the original intact tablet as it appeared before ingestion and the essentially intact tablet and the large fragments of the other tablet that were isolated from the feces. After photographing, the drug content of the material isolated from the feces was determined. The essentially intact tablet isolated from the feces assayed 489 mg. (98% of labeled dose), and the fragments[2] of the other tablet assayed 240 mg. (48% of labeled dose).

It is obvious that an enteric-coated tablet that gave zero plasma levels of bioactive aminosalicylate and that was excreted in the feces would be clinically ineffective. It would be unethical to perform a clinical study in patients with tuberculosis to prove such a point. The results obtained are attributable to both poor disintegration of the tablets and slow dissolution of drug from the fragments of the tablets once they did disintegrate or the coating ruptured. This was readily

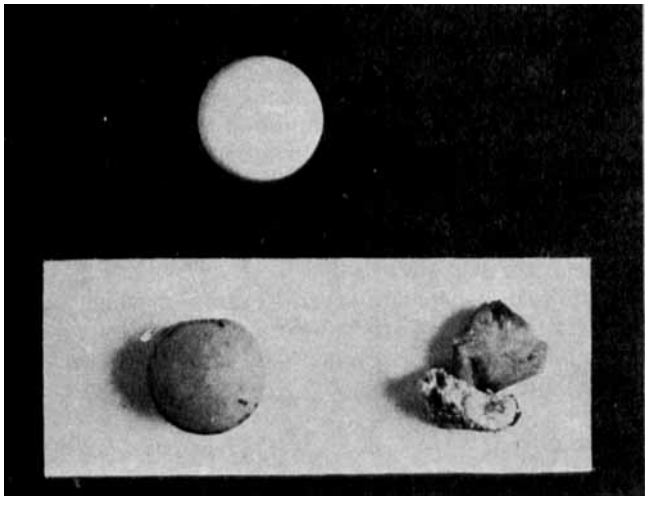

Figure 1—*(Top) Enteric-coated tablet before ingestion. (Bottom) Enteric-coated tablets excreted in the feces.*

[1] 4-Aminosalicylic acid; Parasal enteric-coated 0.5-g. tablet (Lot No. 722165B), containing 0.5 g. aminosalicylic acid USP (Panray Division of Ormont Drug and Chemical). The other dosage forms had the same trademark and were made by the same manufacturer.

[2] Only some fragments were recovered. Since some remained in the feces, the assay is lower than it should be.

shown by subjecting the tablets to *in vitro* test conditions in which the intensity of agitation was very much less than exists during performance of the USP tablet disintegration test. The flask and stirrer method of Poole (1969), as described by Wagner (2), was employed. For the first 0.5 hr., the tablets were subjected to 0.1 *N* HCl with a stirring rate of 50 r.p.m. For the remainder of the test, the tablets were stirred in pH 6.9 buffer, first at a stirring rate of 50 r.p.m. and then at a stirring rate of 200 r.p.m. Three of the enteric-coated tablets tested under these conditions exhibited initial cracks in the coatings after 230, 290, and 300 min. at 50 r.p.m. and then slowly released 22.7, 24.0, and 24.0% of the labeled dose over additional periods of 160, 60, and 40 min., respectively. When the stirring rate was increased to 200 r.p.m., these tablets eventually released essentially the labeled dose of drug. A fourth tablet, tested under the same conditions, showed no release of drug after 420 min. at 50 r.p.m.

Under the same conditions, the sodium aminosalicylate solution, when added to acid such that the final concentration was 0.1 *N* HCl, showed no precipitation of aminosalicylic acid (*i.e.*, infinite rate of dissolution). The suspension gave apparent first-order dissolution in 0.1 *N* HCl at 50 r.p.m., with a rate coefficient of 4.28 $hr.^{-1}$; at the end of 30 min., an average of 89.0% of drug was in solution (average of five tests). The compressed tablet similarly released drug in 0.1 *N* HCl at 50 r.p.m., with a coefficient of 2.58 $hr.^{-1}$; at the end of 30 min., an average of 71.3% of the labeled dose of drug was in solution (average of four tests with individual tablets). The enteric-coated tablets did not disintegrate in the classical sense when stirred at 50 r.p.m. in the pH 6.9 buffer. The coatings merely cracked open, and the drug was released extremely slowly from the ruptured tablets. It was not until the stirring rate was increased to 200 r.p.m. that the tablets really disintegrated and eventually released their labeled content of drug. These results strongly suggest that the intensity of agitation in the USP tablet disintegration test is too intense, at least for enteric-coated aminosalicylic acid tablets, and that the USP test does not predict performance in man. Thus, this is a documented case where a commercial product met compendia standards but was not suitable from a standpoint of effectiveness.

Feldmann (3) stated: "In other words, from a statistical viewpoint, the number of cases in which products have been found to meet compendia standards, but are not suitable from the standpoint of effectiveness or safety, are negligible."

Historically there are several examples which could be used to challenge the above quotation, but in this communication we document an example discovered in our laboratory.

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JOHN G. WAGNER▲
PAUL K. WILKINSON
ALLEN J. SEDMAN
ROGER G. STOLL
College of Pharmacy and
Upjohn Center for Clinical Pharmacology
University of Michigan
Ann Arbor, MI 48104

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▲ To whom inquiries should be directed.

Editor's note: The number of different drug products on the U. S. market has been estimated at somewhere between 100,000 and 300,000. A most conservative estimate would be that one batch or lot has been produced annually of each product over the 5-year period between the quoted testimony and Dr. Wagner's report of the faulty lot of aminosalicylic acid tablets. This amounts to a defect rate of one lot out of a total of ½ million to 1½ million batches of drug products. As Dr. Wagner notes, there have been several such reports, probably raising the number of defects to five or perhaps 10; even this upper figure would give a defect ratio of approximately 1:100,000. We are grateful to Dr. Wagner for confirming our hypothesis that from a statistical viewpoint such incidences indeed are negligible. —EGF

Reliable and Simple Method of Intravenous Injection into the Laboratory Rat

Keyphrases ☐ Injection techniques, intravenous—use of dorsal penis vein, rats ☐ Drug administration—intravenous injection *via* dorsal penis vein, rats ☐ Intravenous injection of drugs into small laboratory animals—dorsal penis vein method

Sir:

In a previous article, Salem *et al.* (1) demonstrated a technique for intravenous injection of drugs into small laboratory animals *via* the dorsal penis vein. The advantages of this procedure compared to the tail vein method (2) lie in its simplicity, rapidity, reproducibility, and ease of injection. Tail vein injections into rats weighing over 100 g. are usually difficult and poorly reproducible, and they generally require a great degree of skill. On the other hand, the dorsal penis vein technique requires very little prior experience, so a relatively untrained laboratory worker can master the procedure in a short time, *i.e.*, one to two trials. In addition, tissue damage at the site of injection will have a minor overall effect on the animal compared to intracardial injection, and surgical manipulations such as those involved with femoral vein injections (2) are not required.

Due to these advantages it is not surprising that this method of drug administration is being employed in biopharmaceutical and pharmacokinetic studies. A review of the literature indicates that little information has been published concerning the physiological fate of drugs administered *via* this route. It is important to know whether this vein is part of the portal or general circulation. Drugs administered orally or intraperitoneally are absorbed *via* the mesentery blood system. These vessels combine to form the portal vein which leads directly to the liver. The drug plasma concentra-