## Correspondence

### Case history of a pharmaceutical formulation failure

*To the Editor:*

The formulation of pharmacologically active substances (drugs) into therapeutically effective pharmaceutical dosage forms requires considerable scientific skill, one which is not shared equally by all manufacturers. Consequently, certain pharmaceutical dosage forms containing the same drug may differ appreciably in therapeutic efficacy.[4, 6, 9] Two and three years ago, reports from this and other laboratories directed attention to the lack of adequate physiologic availability (i.e., absorbability) of aspirin from a widely used enteric-coated tablet product produced by a major pharmaceutical manufacturer.[1, 2, 8] In our own study, absorption of aspirin ranged from 0 to 25 per cent of the administered dose in 3 out of 4 subjects.[8] The tablets were noted on occasion to appear intact in the stool and yielded poor therapeutic results.[1] Nevertheless, they passed the U.S.P. tablet disintegration test and contained the labeled amount of aspirin.[8] Significantly, there was an indication that at least one other enteric-coated tablet preparation (thyroid) made by the same manufacturer was also clinically ineffective and that intact tablets were passed in the stool.[1] The manufacturer did not withdraw either product from the market, nor was there any apparent action by the Food and Drug Administration, despite the several adverse reports from different laboratories.

The recent adoption by this manufacturer of a tablet identification imprint for his products presented an opportunity to re-evaluate the physiologic availability of his enteric-coated aspirin tablets with the certainty that the particular tablets used in the study were of recent manufacture. They were obtained directly from a wholesale house and there was no indication that they had been exposed to adverse storage conditions. The determination of physiologic availability was carried out in 6 healthy male volunteers, 23 to 29 years old. The experimental design and methods were the same as in the previous study,[8] except that single tablets and 0.32 Gm. aspirin in solution were given. Results are summarized in Fig. 1 and show that absorption occurred only 7 to 19.5 hours (average, 13.6 hours) after administration and that it was so slow as to be therapeutically ineffective. After 24 hours an average of only 28 per cent (range, 2 to

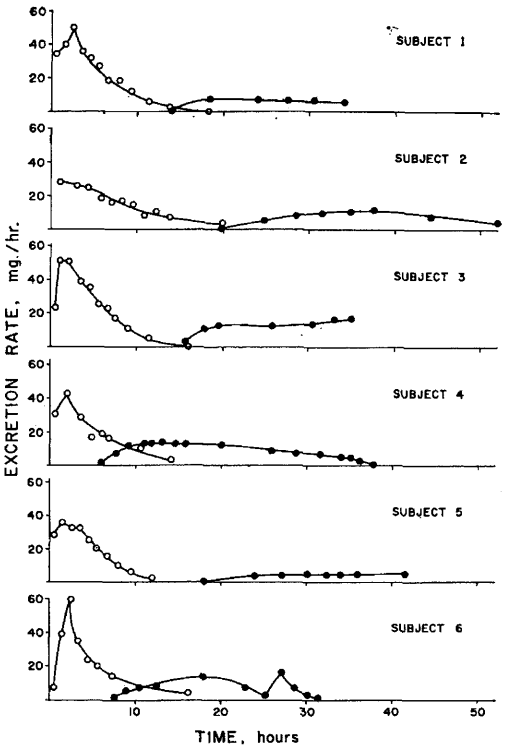


**Fig. 1.** Urinary excretion rate of total salicylates as a function of time after oral administration of 0.32 Gm. aspirin in solution (○) and in an enteric-coated tablet (●) to 6 healthy adult male subjects.

64 per cent) of the administered dose had been recovered in the urine from the enteric-coated tablets; recovery of salicylate from solution was essentially complete by that time (average, 95 per cent; range, 92 to 98 per cent). The relatively constant and prolonged rate of salicylate excretion from the enteric-coated tablets suggests that the drug diffused slowly through an essentially intact coating (i.e., a surface of relatively constant area), and that the tablets did not disintegrate in the intestinal tract. Properly formulated enteric-coated tablets do not release drug in the stomach but do so promptly after passage into the small intestine and yield measurable salicylate levels in the plasma within 2 hours after administration.[3] The tablets used in the present study passed the U.S.P. tablet-disintegration test in that they resisted disintegration in simulated gastric fluids for more than one hour and disintegrated within 20 to 25 minutes in simulated intestinal fluid (U.S.P. limit, 125 minutes).

The results of this study illustrate several important but not generally appreciated facts which have bearing on the present controversy concerning generic vs. brand name prescribing:

1. The therapeutic efficacy of a pharmaceutical product is a function not only of its active ingredient(s) but also of the design and properties of the dosage form.
2. Different pharmaceutical products containing the same kind and amount of drug may differ appreciably in efficacy.
3. Ineffective (improperly formulated) products are marketed occasionally (the incidence presently being unknown due to lack of sufficient studies) by major "brand name" pharmaceutical manufacturers[4, 6, 9] as well as by smaller companies specializing in low cost generic products. (For other examples, see references 4, 6, and 9 and 5, 7, and 11.)
4. At present, the U.S.P. and N.F. do not provide suitable standards to assure the physiologic availability of the products listed in these compendia.[10]
5. There is now at least one example of lack of appropriate action by a major pharmaceutical manufacturer as well as the Food and Drug Administration during more than two years after reports in the literature which demonstrated clearly the lack of adequate absorption and the resulting therapeutic ineffectiveness of a clearly identified pharmaceutical product.

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### *References*

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