lubricating property. Polytetrafluorethylene tablet punches were prepared from $^{5}/_{8}$-inch rods and used in conjunction with a $^{5}/_{8}$-inch metal die on the single punch machine. Sticking and picking were almost completely eliminated, but the operation was complicated by the tendency of this plastic to deform under pressure (a phenomenon known as "cold flow"). The punch area that entered the die retained its shape, but the shaft of the punch was deformed and buldged outwards. It was then reasoned that if faces of metal punches were tipped or coated with polytetrafluorethylene, the plastic would be confined within the die cavity during compression, thus preventing deformity. Coating the punch by spraying a thin layer of polytetrafluorethylene was somewhat effective; however, on extended tableting runs the material peeled off. Punches for the single punch machine were subsequently modified by bonding a small polytetrafluorethylene tip to the surface. The tableting operation using the latter punches was quite satisfactory and similar punches were modified and successfully used for the larger production equipment. The use of this device has eliminated much of the difficulty previously experienced with the manufacture of this product.

Several disadvantages were observed during the use of polytetrafluorethylene tipped punches. They are easily damaged and are subject to tip deformity and breakage. Because of the tendency of this plastic to deform under pressure, only flat faced or at most a slightly beveled tablet can be produced with these punches. Monogramming is obviously not practical. Nevertheless, for our specific problem polytetrafluorethylene tipped punches performed satisfactorily under production conditions.

Bonding Polytetrafluorethylene to Punch Surfaces.—Polytetrafluorethylene is not easily bonded to metal surfaces and requires a series of operations to produce a firm seal. An accepted procedure to facilitate bonding is to etch the surface of the plastic with molten sodium and cement it under high pressure to the metal surface by means of an epoxy resin cement. Tipped punches prepared in this manner were satisfactory but were subject to cleavage of the plastic component from the metal surface after a period of use. Modification of the bonding technique by first spraying the punch surface with a layer of pure molybdenum in order to produce a rough surface for greater plastic adherence significantly reduced this breakage (5).

SUMMARY

A method has been developed for preparing by direct compression a large effervescent tablet containing a mixture of sodium isoascorbate and isoascorbic acid which dissolves to form a solution free of turbidity or haze. The use of tablet punches tipped with polytetrafluorethylene has successfully circumvented the major problem of sticking and picking associated with the manufacture of this product.

The utilization of polytetrafluorethylene tipped punches may find application in other tablet formulations exhibiting similar difficulties. In addition, preliminary experimentation with this device has been successful in reducing lubricant levels in certain tablet blends and further investigation in this area is warranted.

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Communications

Inactive Prednisone Tablets U.S.P. XVI

Sir:

We wish to report a case in which prednisone tablets meeting U.S.P. XVI specifications were found to be clinically inactive *in vivo* and some *in vitro* test results which suggest a possible reason for their inactivity.

A 25-year-old white married female of Mediterranean ancestry has been under the care of one of us (FAC) for approximately 5 years. Her clinical diagnosis was familial Mediterranean fever with repeated episodes of clinical peritonitis confirmed by laboratory studies and previous surgical exploration. The prompt use of oral prednisone in amounts of 20 mg. in a 24-hour period for the first 2 or 3 days would promptly abort the clinical symptoms, the laboratory findings of leukocytosis, etc., changing only slightly. The patient's prescriptions had been written with the generic name "prednisone." On one occasion, after 72 hours of 5 mg. four times a day, the patient had no clinical effects from the medication. It was discovered at that time that a different "brand" of prednisone had been dispensed than that previously used. The patient was immediately transferred to the brand of prednisone used previously and again within 24 hours there was almost complete resolution of the clinical syndrome.

The manufacturer's reassay of tablets, from the same lot as the tablets which were ineffective in treatment of the condition described, indicated that they contained essentially all of their labeled content. Also, the tablets passed the

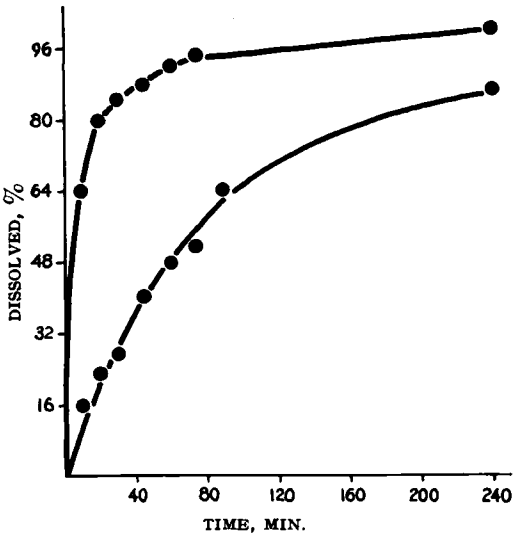

Fig. 1.—Cumulative per cent prednisone tablets dissolved *vs.* time from clinically active (upper curve) and inactive (lower curve) tablets of this substance.

U.S.P. XVI disintegration time test well within prescribed limits.

A small number of tablets were obtained from the manufacturer for a more detailed examination of their physical properties. The U.S.P. XVI disintegration time test was repeated in one of these laboratories and all the tablets had disintegrated within 6 minutes. It was observed, however, that large particles of the tablets remained on the bottom of the test beaker used in the procedure. In addition, during the conduction of the test it appeared that the disk used in the apparatus formed the large particles and subsequently forced them through the screen at the bottom of the testing tubes. One tablet was subjected to the disintegration time test without the disks and at 25°. The tablet had not disintegrated within 1 hour but had disintegrated within 2 hours.

In order to study the problem further, the remaining tablets were examined by means of a dissolution rate test. For comparison, tablets of the brand (which also disintegrated in less than 6 minutes in the U.S.P. XVI test) which gave a satisfactory clinical response were also subjected to the same test. The solution rate test conditions and apparatus used were those described by Levy and Hayes (1). The dissolution media were 500 ml. of water maintained at 37° and aliquots of it were assayed spectrophotometrically at 240 mμ for drug content at various times.

Figure 1 shows cumulative per cent of drug released from the two brands of tablets tested.

TABLE I.—SUMMARY OF DISINTEGRATION AND SOLUTION RATE DATA

Prednisone Tablets	U.S.P. XVI Disintegration Time (with disk)	Disintegration Time (without disks)	Av. time for 50% of Drug to Dissolve, ± S. D. Dev.
Active lot	<6 min.	<6 min.	4.3 ± 1.3 min.
Inactive lot	<6 min.	1–2 hr.	100 ± 53 min.

It is apparent from this figure that the tablets which were clinically ineffective dissolved much more slowly than the effective ones. The effective tablets released 50% of their content more than 20 times as rapidly as the ineffective ones.

Each point on the curve of Fig. 1 showing dissolution rate behavior of the clinically effective tablets is the average of six determinations. In the case of the ineffective brand, each point is the mean of three determinations. It was observed that the release of prednisone from the ineffective tablets was much more erratic in regard to tablet-to-tablet variation than from the effective brand of tablets. The various data obtained in this study are summarized in Table I.

This study provides additional evidence to previously published work (1–8) suggesting that the U.S.P. disintegration time test should be re-evaluated as a method to predict correctly physiological availability *in vivo*. The fact that a dissolution rate test gave results that appeared to be in qualitative agreement with clinical experience does not mean that the particular test used will necessarily be applicable to predict physiological availability from tablets of other drugs.

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F. A. CAMPAGNA
GLENN CURETON†
R. A. MIRIGIAN‡
EINO NELSON§

2166 Hayes Street
San Francisco, Calif.
† Harvard University
Boston, Mass.
‡ School of Pharmacy
University of California Medical Center
San Francisco
§ School of Pharmacy
State University of New York at Buffalo
Buffalo 14

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