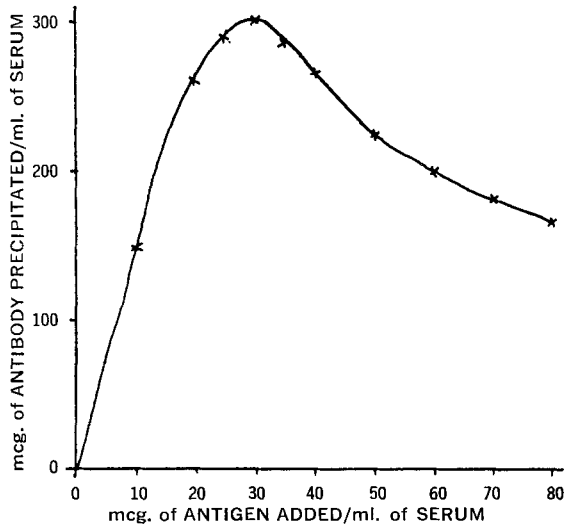

Figure 1—*The precipitin curve.*

tyrosine, have been shown to be antigenic (1–3). However, due to the unknown primary amino acid sequence of these random polymers, it is difficult to describe the locus of the active site of these antigenic polymers. To overcome this difficulty, the use of linear polypeptides with a known repeating sequence of amino acids has been suggested. For this purpose, poly-(L-tyrosyl-L-glutamyl-L-alanylglycyl)glycine-1-^{14}C ethyl ester was recently synthesized (4), and we wish to report the antigenic properties of this polymer.

After obtaining preimmunization sera, four rabbits were treated at weekly intervals with 500 mcg. of poly-(tyr-glu-ala-gly)gly-1-^{14}C ethyl ester. The first 2 weeks they were injected intradermally using complete Freunds adjuvant as suspension medium, and the 3rd week they were injected subcutaneously. The injection on the 4th week was done intravenously using buffered saline. Bleedings were conducted on the following week, and the serum from each animal was found to give a precipitin reaction with the polymer. The preimmunized sera under the same conditions gave a negative precipitin reaction. The quantitative determination of the antibody was obtained by the addition of dilutions of poly-(tyr-glu-ala-gly)gly-1-^{14}C ethyl ester to 1-ml. samples of the pooled rabbit sera. The precipitates were kept at 4° for 48 hr., washed twice with small volumes of buffered saline, and collected by centrifugation. The total amount of protein precipitated was estimated by analysis for nitrogen by a micro-Kjeldahl method (5). The amount of antigen contained in each precipitate was estimated by use of the Folin-Ciocalteu method. From these results the precipitin curve shown in Fig. 1 was obtained.

From these results it can be seen that this polypeptide is antigenic; further studies pertaining to the specificity of its antibodies are presently in progress.

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Received December 8, 1969.

Accepted for publication February 3, 1970.

Presented in part at the 158th American Chemical Society National Meeting, New York, N. Y., 1969.

After submission of this manuscript, a review article by M. Sela, *Science*, **166**, 1365(1969) was published on the molecular aspects of antigenicity.

This work was supported by a grant from the National Science Foundation.

We wish to thank Dr. R. D. Stollar of Tufts Medical School for many helpful suggestions.

Quantitative Correlation of Absorption and *In Vitro* Dissolution Kinetics of Aspirin from Several Dosage Forms

Keyphrases ☐ Aspirin dosage forms—dissolution, absorption ☐ Absorption–dissolution, aspirin—correlation

Sir:

Several types of *in vivo–in vitro* correlation are described in the pharmaceutical literature (1). The most informative of these, but the most difficult to achieve, is the quantitative correlation between *in vitro* dissolution and *in vivo* absorption, particularly one involving several different dosage forms. An example is found in the report of Levy *et al.* (2) who were able to correlate the absorption of aspirin from three different dosage forms with a function of the dissolution rate, using the beaker method (3) at 50 r.p.m. A plot of the percent absorbed at time *T versus* the percent dissolved in (*T*-lag time)/2 gave a straight line with a slope of unity.

The present report introduces a new dissolution method, which has permitted an absolute quantitative correlation between the absorption and *in vitro* dissolution of aspirin from these three dosage forms. These findings extend the work of Levy *et al.* (2) because this type of 1:1 correlation was not attainable with the beaker method.

A schematic diagram of the rotating-flask apparatus used to determine dissolution is shown in Fig. 1. The apparatus consists of a spherical glass flask suspended in a constant-temperature bath. The globe is supported by glass rods, fused to its sides, which form the horizontal axis of the sphere. One support rod is coupled to a constant-speed motor, which provides rotation about the horizontal axis. A sampling port is molded into the sphere to permit introduction of the dosage form and periodic withdrawal of samples. The volume of the dissolution medium (in this case 400 ml.) and the position of the sampling port are such that fluid

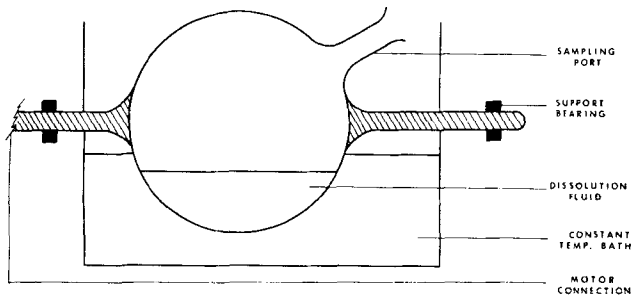

Figure 1—*Schematic diagram of dissolution apparatus. The flask has a diameter of about 16 cm. (6.5 in.)*

does not enter the port, regardless of the position of the flask as it proceeds through a revolution. These measures prevent the accumulation of undissolved solid in the port. The port is stoppered to prevent loss of the dissolution medium to the water bath. A review of the literature on dissolution methodology suggests that this method is unique, although the hydrodynamics of the present system may be similar to that found in the apparatus described by Ferrari and Khoury (4) or in the apparatus utilized by Simoons (5).

The dissolution rate of aspirin from three commercially available dosage forms—conventional tablets, buffered tablets, and timed-release tablets—was determined at 37° and 1.2 r.p.m. in 0.1 *N* HCl. Samples of the dissolution fluid were taken at frequent intervals by means of a filter pipet. The samples were then hydrolyzed and assayed spectrophotometrically at 302.5 mμ for salicylic acid. The dissolution data on each dosage form were compared with percent absorbed–time data on the same dosage forms in man from the literature (2, 6). The correlation is shown in Fig. 2 which is a plot of percent absorbed to time *T versus* percent dissolved *in vitro* at time *T*. Regression lines, calculated by the method of least squares, using all data were as follows:

$$\text{percent absorbed} = 0.79\,(\text{percent dissolved}) + 2.44 \quad \text{(Eq. 1)}$$

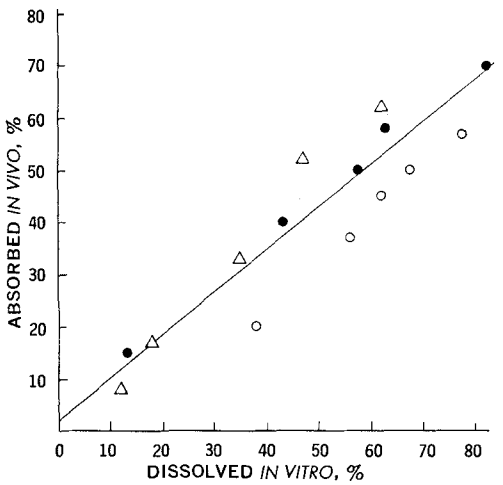

Figure 2—*Plot of percent of dose of aspirin absorbed to time* T *after drug administration* versus *percent dissolved* in vitro *at time* T. *Key:* ○, *conventional tablets;* ●, *buffered tablets, and* △, *timed-release tablets.*

$$\text{percent dissolved} = 1.08\,(\text{percent absorbed}) + 4.48 \quad \text{(Eq. 2)}$$

The solid line in Fig. 2 represents Eq. 1. Using the method described by Mather (7) for interclass correlation where both variables are normally distributed, the correlation coefficient was found to be 0.92 corresponding to $p < 0.001$.

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Received November 21, 1969.
Accepted for publication January 29, 1970.
Supported in part by Grant AM-11498 from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

* Fellow of the American Foundation for Pharmaceutical Education.

Penicillin Stability to Alcohols

Keyphrases □ Penicillin G, potassium, stability—alcoholic solution □ Stability—alcoholic potassium penicillin G solution

Sir:

There is considerable confusion in the literature with regard to the stability of penicillin solutions in the presence of alcohols. Several textbooks and other published works state that penicillin solutions are inactivated by alcohols and glycerol (1–14), and this statement is also found in the most recent volume of the *United States Pharmacopeia* under the monograph for Potassium Penicillin G (15). Perhaps because of this statement, at least one textbook on microbiology cautions that patients with venereal disease being treated with penicillin should avoid an intake of alcoholic beverages (16). Historically, one can trace the probable origin of the belief that penicillin is inactivated by alcohols to a report by Abraham and Chain (17) who reported in 1942 that alkali salts of penicillin rapidly lose their biological activity when dissolved in primary alcohols. Presumably, alcoholysis proceeds with the ultimate formation of the appropriate inactive monoester of penicilloic acid (Scheme I).

However, in 1948, Chain *et al.* (18) conclusively demonstrated that this decomposition of penicillin