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Generic Tolbutamide Tablet Dissolution: Intralot and Interlot Variation

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Abstract □ Dissolution profiles for 62 lots of tolbutamide tablets from six manufacturers have been characterized using the USP paddle-stirrer apparatus. Results of paddle-stirrer dissolution for percent drug dissolved at 10, 20, and 30 min correlated well ($r^2 = 0.7444$) with results from the USP rotating-basket test for 39 lots of tolbutamide. Interlot and intralot variability in tolbutamide dissolution was highly dependent on the manufacturer. For one product, the intralot range (for six paddle-stirred tablets) of percent drug dissolved after 30 min was 50–68% while the maximum interlot range for mean dissolution was 58–104%. One lot failed to meet both the rotating-basket and the paddle-stirrer dissolution specifications. Tablet response to aging at 60, 75, and 98% relative humidity over time was also highly manufacturer specific. The innovator's product repeatedly dissolved well when fresh or aged at all humidities. Dissolution from some generic tablets was dramatically depressed by humidity aging, even after only 3 d. Pretreatment of tablets with simulated gastric fluid modified the dissolution profile of one poorly dissolving lot of tablets. Results indicate that manufacturing quality control is highly variable among tolbutamide tablets.

Keyphrases □ Tolbutamide—dissolution, intra- and interlot variation, effect of humidity aging □ Dissolution studies—tolbutamide, intra- and interlot variation, effect of humidity aging

Tolbutamide tablets must meet United States Pharmacopeia (USP) dissolution requirements which are established because ". . . in many cases it is possible to correlate dissolution rates with biological availability of the active ingredient" (1). Dissolution testing is also recognized (2) as useful for quality control purposes.

Tolbutamide exhibits only limited solubility and the United States Food and Drug Administration (FDA) recognizes that tolbutamide products are prone to bioavailability problems. Currently, the FDA lists 12 manufacturers' products as "therapeutically equivalent to each other" (3). Large variations in lot-to-lot dissolution of tolbutamide products indicate variations in quality and possible variations in bioavailability since low tolbutamide bioavailability is sometimes related to poor tolbutamide tablet dissolution (4–6). If such variations occur for different lots of products which have been ruled "therapeutically equivalent" by the FDA, then satisfaction of current FDA regulations may not assure lot-to-lot equivalence of products on the FDA list.

Previous work has shown extensive lot-to-lot variation in dissolution of tolbutamide tablets for six lots of one manufacturer (7), while there was uniformity for the originator's product. Others have demonstrated that humidity "aging" of tolbutamide tablets differentially affected dissolution for two different brands of products (8). Also, the physiological exposure to acid of ingested tablets is not mimicked by the current USP dissolution test although exposure of tolbutamide tablets to gastric acid has been reported to be necessary for disintegration and dissolution of some formulations (9).

Therefore, the purposes of this study were: (*a*) to evaluate the dissolution characteristics of several fresh lots of tolbutamide listed as therapeutically equivalent by the FDA; (*b*) to evaluate many of the same lots after humidity "aging" of the tablets; (*c*) to determine the effect of tablet exposure to gastric acid on tolbutamide dissolution for both fresh and humidity-aged tablets.

EXPERIMENTAL SECTION

Products were obtained commercially, stored in tightly closed, opaque containers in the dark at room temperature for 1–3 months, and tested using the USP rotating-basket (10) or paddle-stirrer dissolution test (1). Samples (3 mL) were collected with a continuous flow (set at 5–10 mL/min) eight-channel peristaltic pump[1] fitted with stainless steel 20–30 μm in-line filters. Samples were collected for 6 tablets for 10, 20, 30, and 45 min for the rotating-basket test (150 rpm) and at 10, 20, and 30 min for the paddle-stirrer test (75 rpm) in order to establish a dissolution *versus* time profile (rather than single time point dissolution values). All samples were replaced with temperature-equilibrated dissolution medium.

Filtered samples were diluted, the UV absorbance was measured at 226 nm (1), and the concentration of tolbutamide was calculated based on a seven point standard curve prepared the same day as unknowns were collected. Standard curves were generated by preparing known concentrations of either USP reference standard or company-provided tolbutamide. The UV spectra from these sources were superimposable and the standard curves considered equivalent as the null hypothesis of equal slopes and intercepts could not be rejected ($\alpha = 0.05$). Standard curves were fit with parabolic regression and had coefficients of variation of <4%. The average inversely estimated percent

[1] Gilson minipuls 2, eight channel peristaltic pump; Gilson Medical Electronics, Middleton, Wis.

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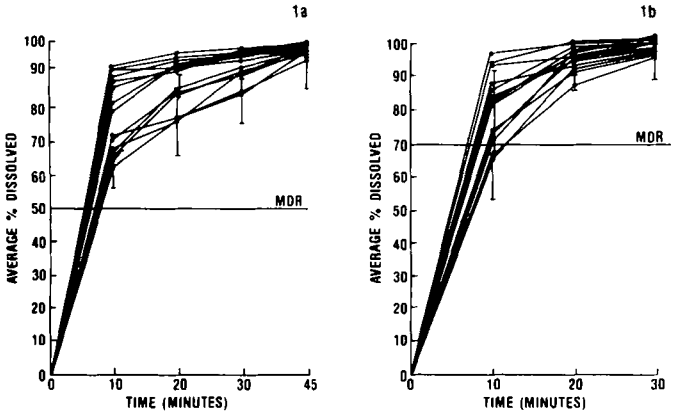

Figure 1—*Average percent of labeled tolbutamide dissolved from 500 mg of U tolbutamide tablets using the rotating-basket test (a) and the paddle-stirrer test (b). MDR is minimum dissolution requirement. Each data point is the average of six tablets and each line is for a different test (Table I). Data variation bars show the range of observed values for the slowest dissolving lots.*

of theory for standard concentrations was 100 ± 0.5% and all individual concentrations were estimated within 3% of theoretical values. The use of UV absorbance as a measure of dissolved tolbutamide was considered appropriate as HPLC analysis (11) of 37 different lots of tolbutamide resulted in only one absorption peak with a retention time equal to that of standard tolbutamide. Content analysis of these lots by HPLC also gave the same results as UV analysis which indicates that the only UV-absorbing material released was tolbutamide.

Humidity aging of tablets was accomplished by manipulating water vapor pressure in closed tanks using saturated salt solutions (12). Standard all-glass aquariums (50 × 26 × 30 cm) with glass covers were used for constant humidity chambers. A saturated solution of potassium sulfate was prepared in deionized, distilled water and placed in the bottom of the tank to a depth of 2–3 cm (~2.6 L) to produce 98% relative humidity (rh). Solutions of sodium dichromate or potassium carbonate were used for 60% rh and sodium chloride was used for 75% rh. A galvanized rack was placed in the tank to hold aluminum foil-lined petri dishes 7 cm above the surface of the liquid. Air circulation was maintained within the tank by a small electrical fan mounted inside the tank. Humidity was monitored daily with a wet and dry bulb hygrometer. No attempt was made to regulate temperature within the chambers as temperature variability within the laboratory was small and temperature dependence of relative humidity using the salt solutions is small (12). The average relative humidity chamber temperature during the experiments was 20.1°C with a maximum range of 1.1°C. The chamber was made airtight by the use of foam strips impregnated with petroleum as a seal between the glass cover and the aquarium.

Tablets were subjected to the aging process by placing four tablets of each lot in aluminum foil-lined petri dishes without covers, taking care that no tablet

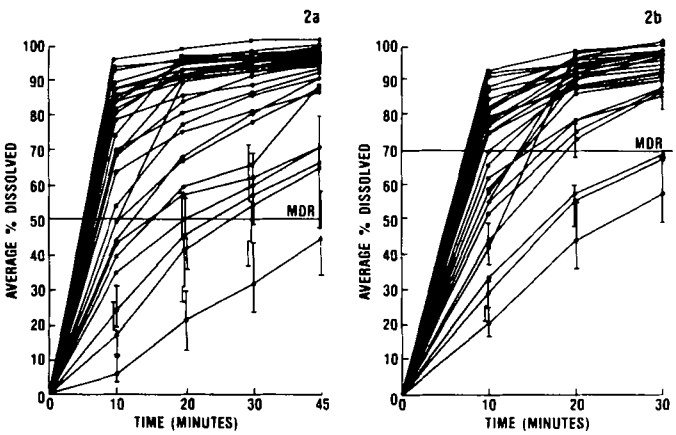

Figure 2—*Average percent of labeled tolbutamide dissolved from 500 mg of P tolbutamide tablets using the rotating-basket method (a) and the paddle-stirrer method (b). Each data point is the average of six tablets and each line is for a different lot, except tablets which failed the test. The lots which failed (2b) are the same lot number of the same manufacturer (P) but distributed under different private labels.*

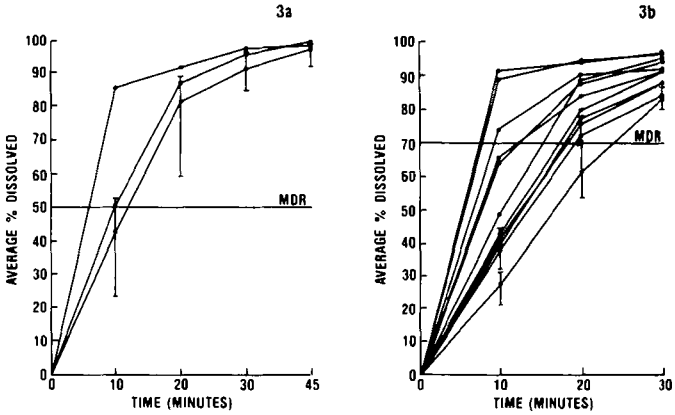

Figure 3—*Average percent of labeled tolbutamide dissolved from 500 mg of M tolbutamide tablets using the rotating-basket test (a) and the paddle-stirrer test (b).*

touched another. The chamber was then sealed and not opened until the end of the aging period.

Dissolution tests wherein the products were exposed to enzyme-free simulated gastric fluid (acid pretreatment) utilized 9.6 mL of concentrated hydrochloric acid per liter of water (pH ~1.1–1.2). Tablets of each product were allowed to separately dissolve, each in 900 mL of the simulated gastric fluid, in a USP rotating-basket apparatus at 150 rpm for 30 min. After 30 min the baskets were raised and allowed to drain. The acid dissolution medium was filtered under vacuum and then the filter paper with any retained solids was placed in a dissolution resin kettle (containing 900 mL of pH 7.4 phosphate buffer) fitted for paddle-stirrer dissolution. The contents of the basket were transferred to the phosphate buffer by gently dipping the basket (using forceps) into the buffer. Then the paddle was lowered and stirred at 75 rpm and samples were collected over time to determine the amount of tolbutamide dissolved.

RESULTS AND DISCUSSION

All lots passed the disintegration, assay, content uniformity, and tablet weight variation tests. However, there was considerable variation in dissolution characteristics among and within some lots.

Figure 1 shows that dissolution of tolbutamide from the innovators' (U) tablets[2] is relatively uniform within and among lots in both the rotating-basket and paddle-stirred apparatus. Figure 2 for the P product[3] shows wide interlot and intralot variation in dissolution. One lot (Fig. 2a) failed the USP rotating-basket test. The same lot number sold under a private label also failed the paddle-stirrer test (Fig. 2b) but passed the rotating-basket test. The cause of this dissolution variation is unknown. This lot is not the one reported earlier which also failed USP requirements (7). Figures 3–4 show dissolution profiles for tolbutamide products of some other manufacturers[4].

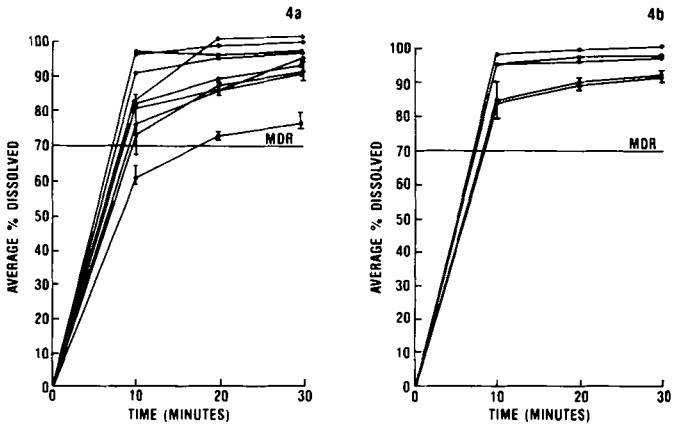

Figure 4—*Average percent of labeled tolbutamide dissolved using paddle-stirrer dissolution from 500 mg of: S, and PH (a); Z (b) tolbutamide tablets.*

[2] Upjohn.
[3] Premo.
[4] Fig. 3, Mylan (M); Fig. 4, Pharmadyne (PH), Smith Kline & French (S), and Zenith (Z).

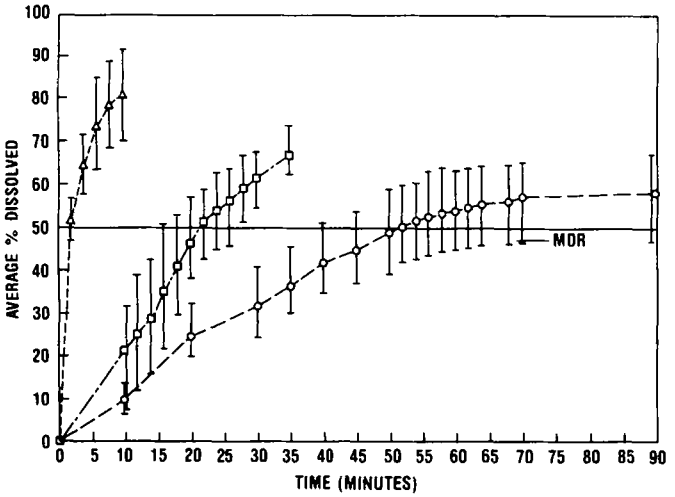

Figure 5—*Percent of labeled amount of tolbutamide dissolved* versus *time using the rotating basket for 6 tablets each of three different lots of product P. Data variation bars are the standard deviation of the mean. These can be compared to ranges shown in Figs. 1 and 2.*

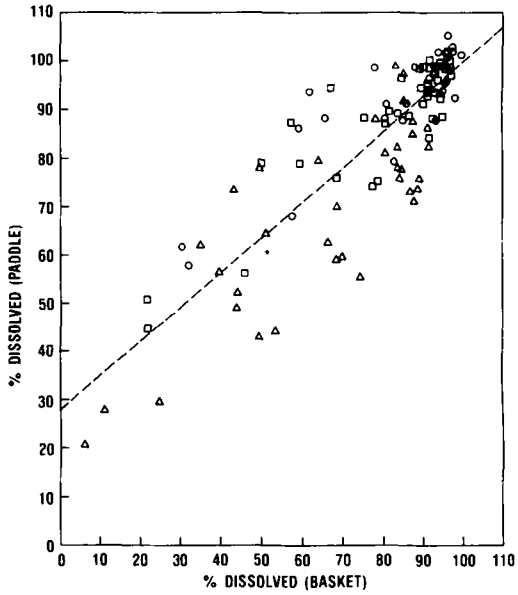

Figure 6—*Comparison of tolbutamide dissolved in paddle stirrer method* versus *rotating basket method. The generated regression line is F(x) = 27.95 + 0.705 x with $r^2 = 0.7444$; r^2 was not improved substantially by fitting to a polynomial of degree two or three. Key: (△) 10 min results; (□) 20 min results; (○) 30 min results.*

It is clear that interlot and intralot variation is manufacturer specific. For example, generic product in Fig. 3b is more variable than product in Fig. 1b, but some of the generic products in Fig. 4 produce dissolution profiles similar to those shown in Fig. 1b. Unfortunately, only a few product lots were available and these were only evaluated according to paddle-stirrer requirements (1). More lots should be tested to fully define the dissolution profiles of these products.

Figure 5 expands the information in Fig. 2a regarding both interlot and intralot variation for product P dissolution. The amount of drug released is highly dependent on the bottle (lot) used and the tablet within a bottle (lot) tested. The time to 50% dissolution was reported by Levy (6) to be related to clinical effectiveness for tolbutamide. The three lots in Fig. 5 required 1.9 min, 21.4 min, and 51.1 min, respectively, to average 50% dissolution in the USP rotating basket test. It must be noted that this test differs from the Levy (6) test, and the 51.1-min dissolution time does not necessarily imply the product will fail clinically. However, slow dissolution with wide intralot and interlot variations in dissolution rate are indicative of degree of quality control (1, 2).

The time to 50% (rotating-basket) and 70% (paddle-stirrer) dissolution for some lots of tolbutamide tested are shown in Table I. Intralot and interlot variability is manufacturer specific. The U product reached 50% and 70% dissolution ~40% faster and with 25–50% of the variation of P and M products. Products U, S, and Z were about equal in time to 70% dissolution, but too few S and Z lots were tested to be conclusive. In general, products dissolving most slowly or most rapidly in the rotating basket also dissolved slowly or rapidly, respectively, in the paddle-stirred test (Table I, Fig. 6) which indicates the two tests are correlated. However, the range of percent dissolved shows more

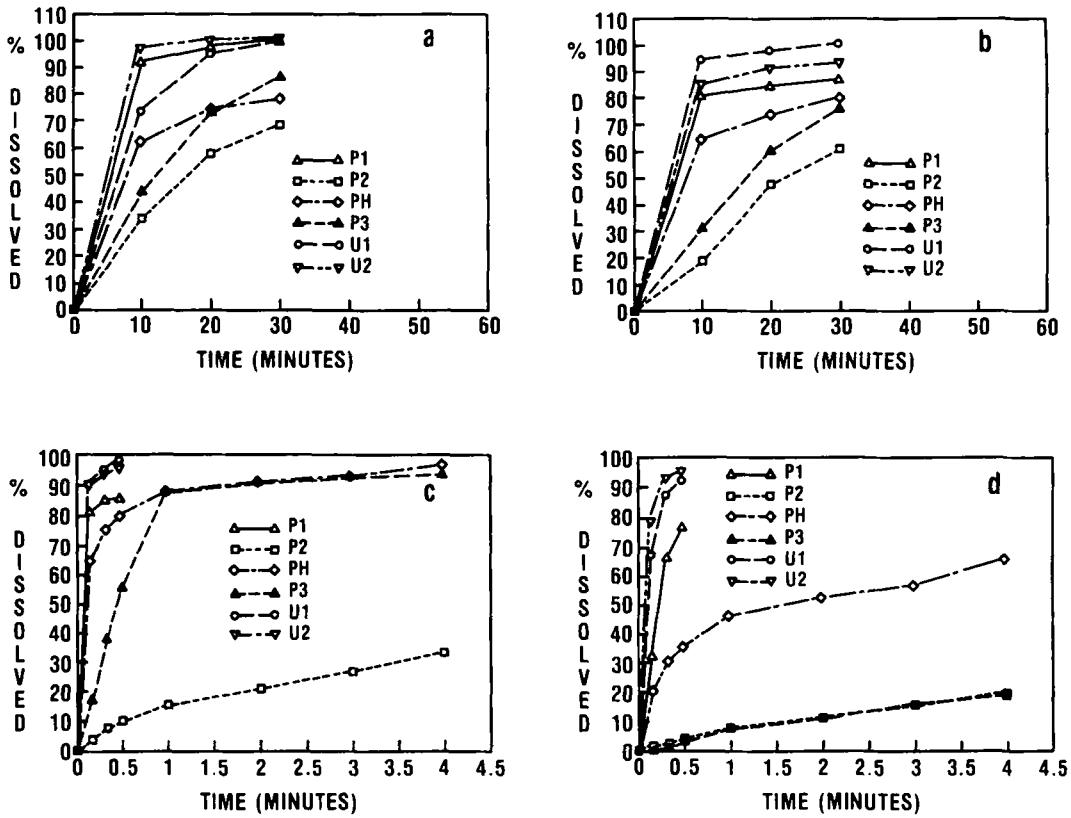

Figure 7—*Effect of 12 weeks of humidity aging on dissolution of P, PH, and U tolbutamide tablets at room humidity and in the closed original container (a), 60% relative humidity (b), 75% relative humidity (c) and 98% relative humidity (d). Key: (△) P1, (□) P2; (◇) PH; (▲) P3; (○) U1; (▽) U2.*

Table I—Time (min) to Reach Compendial Required Dissolution of Labeled Tolbutamide[a]

Product Identification Number[b]	Lot Number	Rotating Basket, 50%[c]	Paddle Stirrer, 70%[d]
U1	495 EP	5.4	7.5
U2	871 FP	5.7	9.9
U3	606 FT	5.6	9.6
U4	461 FU	5.8	7.2
U5	592 FK	5.5	8.2
U6	109 FS	5.5	8.5
U7	740 HR	6.4	8.5
U8	407 HP	6.2	8.4
U9	486 HT	7.6	11.8
U10	926 HY	8.0	7.5
U11	246 JB	7.0	9.4
U12	606 FT	7.3	8.6
U13	461 FU	7.1	8.0
U14	871 FP	7.5	11.6
Mean for U		6.46	8.9
CV, %		14.29	16.06
P1	C80177	6.4	8.0
P2	A80687	5.4	7.2
P3	A80547	15.3	16.3
P4	A80167	20.2	14.8
P5	B80167	14.9	9.5
P6	A90227	6.1	9.6
P7	B90257	7.2	13.9
P8	A80587	23.6	33.5
P9	8111-04	7.8	8.8
P10	B80737	10.3	9.0
P11	A81607	5.9	9.1
P12	B80987	9.4	18.8
P13	810071	10.1	14.9
P14	C81447	5.9	9.2
P15	B80987R	12.4	17.6
P16	810072	6.2	8.8
P17	A80587	26.4	31.9
P17	A80587	54.6	49.7
P18	810073	6.7	13.6
P19	B90367	5.3	7.6
P20	B91517	5.6	9.3
P21	A90737	5.3	7.6
P22	A90787	6.0	8.6
P23	A90757	5.7	8.0
P24	E006D	7.3	13.6
P25	A91157	5.7	8.3
P26	E007D	7.3	10.2
P27	A00258	--	11.6
P28	A00658	—	20.5
Mean Average for P		11.22	14.2
CV, %		92.8	67.35
M1	E011D	5.8	7.6
M2	E010DR	11.6	15.3
M3	E008D	9.8	12.4
M4	G032K	—	12.4
M5	G046D1	—	18.2
M6	E008D	--	17.3
M7	595-215	--	23.8
M8	592-187	—	18.0
M9	607-230	--	9.5
M10	G050D	—	19.3
M11	9M80D	--	7.9
Mean for M		—	14.71
CV, %		—	35.25
PH1	8111-05	7.5	16.2
PH2	8111-06	5.2	8.4
PH3	8111-03	6.0	9.0
Z1	2245-18-1	--	8.3
Z2	2245-18-2	—	8.1
Z3	7181	—	7.2
Z4	2245-03-70	--	7.3
Z5	2245-03-80	—	7.3
S1	BX19409	--	7.3
S2	E060	-	7.7
S3	A29409	—	8.4
S4	A29409	—	8.6
S5	B59409	-	9.6

[a] Estimate based on interpolation between closest time intervals sampled. [b] Product identification: U, Upjohn; P, Premo; M, Mylan; PH, Pharmadyne; Z, Zenith; S, Smith Kline & French. [c] Method requires at least 50% dissolution in 45 min. [d] Method requires at least 70% dissolution in 30 min. Some lots in different-size bottles or received at different times were evaluated twice (U3, U12; U4, U13; U2, U14; M3, M6; S3, S4).

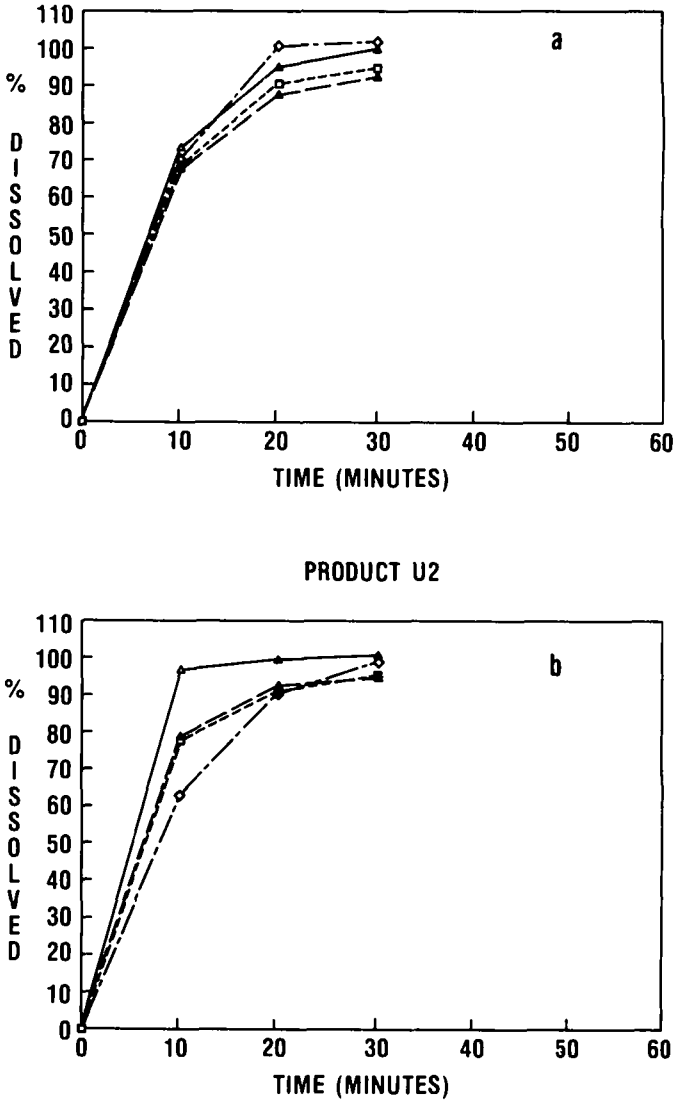

Figure 8—*Effect of aging tolbutamide tablets for various times at 98% relative humidity for two lots (a, b) of U products. Key: (△) fresh; aged (□) 3 weeks, (◇) 6 weeks, (▲) 12 weeks.*

variation in the basket-stirrer tests at each sampling time. This may be because more rapid dissolution occurs with paddle stirring and there is a natural compression of the possible range of percent dissolved drug on the upper end (*i.e.*, 100% is an upper boundary). Thus, one comparative effect is that intralot variation is compressed or more difficult to identify in the paddle-stirring test than in the rotating-basket test.

Khalil *et al.* (8) reported that humidity aging may be used to identify tolbutamide tablets which were not equivalent in their dissolution responses. The effects of humidity aging on tolbutamide lots selected for a paddle-stirrer dissolution study (based on their range of dissolution profiles when fresh) are shown in Fig. 7. Dissolution profiles of U tablets were little affected by aging ≤12 weeks at rh values of 60, 75, or 98%. The other manufacturers' products were not affected by 60% rh, but two lots failed the dissolution test after 75% and three lots failed after 98% rh. Lots P2 and P3 failed to pass the test even after 18 h of dissolution following 12 weeks at 98% rh; these tablets remained intact, or nearly intact.

Figures 8 and 9 show the combined time and rh effects on tablet dissolution. The U products were only slightly affected for all times at 98% rh (Fig. 8b). Lesser effects occurred with 60 and 75% rh. For P and PH products, 98% rh aging variously affected dissolution depending on the lot (Figs. 9). Both 60 and 75% rh affected lot P2 but not lot P1 tablets (Figs. 10). The reason for this lot-specific variable response is unknown. The *CV* for percent tolbutamide dissolved at all rh values is low when the percent of labeled drug dissolved is high (>90%) and sometimes when the percent is low (<10%). Products that are dissolved 20–80% at any given sampling time show differences in both intralot and interlot variation among manufacturers; the same is seen with unaged tablets. Thus, since the innovator's products (U) dissolve quickly

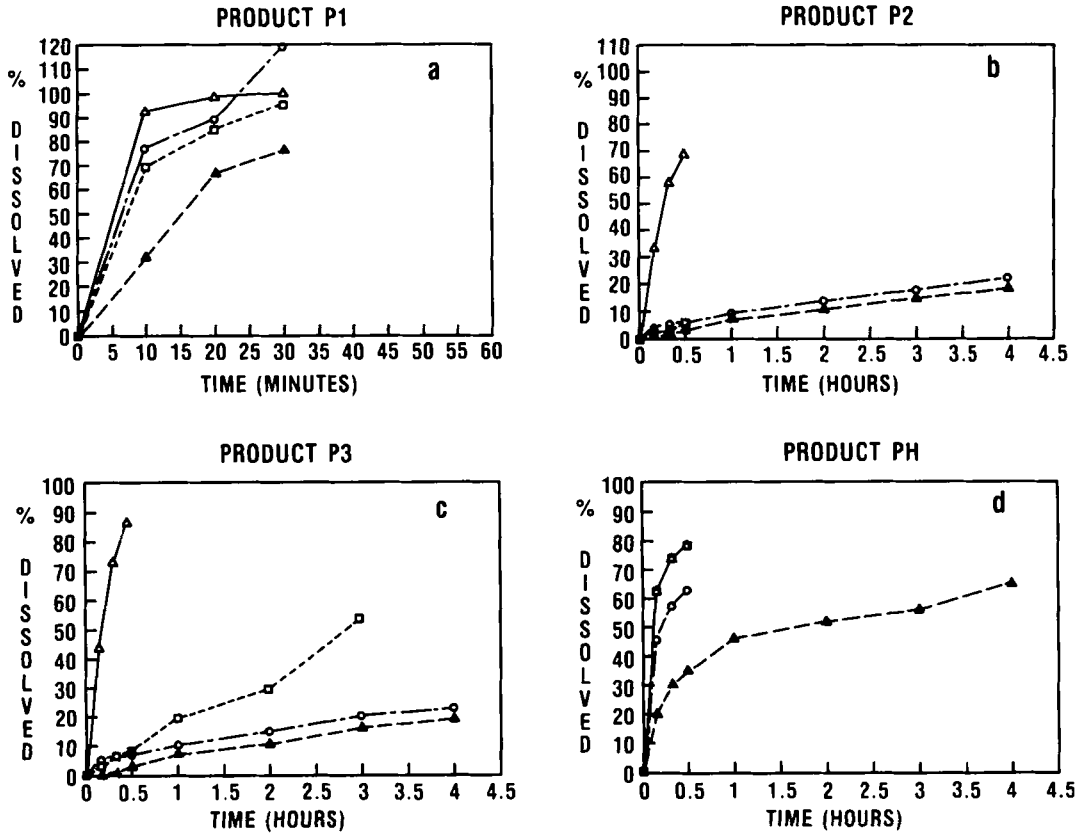

Figure 9—*Effect of aging tolbutamide tablets for various times at 98% relative humidity for P and PH products. P1 (a), P2 (b), and P3 (d) are different lots of P. For PH (d), fresh tablets and tablets aged for 3 weeks aging gave nearly identical values. Key: (△) fresh; aged (□) 3 weeks, (○) 6 weeks, (▲) 12 weeks.*

(>95% after 30 min for fresh and humidity-aged tablets), the dissolution *CV* for U products was generally much lower than for the generic products which dissolved more slowly (for fresh tablets and humidity-aged tablets).

The finding that tolbutamide tablets from different manufacturers and different lots from the same manufacturer did not dissolve equivalently after as little as 3 weeks of aging at different rh values prompted investigation of the effects of shorter exposure. There was no effect on product U (Fig. 11).

Dissolution of P products continued to be variable and effects ranged from marked depression of dissolution (after only 24 h exposure to 98% rh) to virtually no effect, depending on the lot tested. The effects of humidity were lot specific for M (Fig. 12), dramatically depressing dissolution for one lot but not the other. No effect was observed for S products and both lots of Z products were depressed.

One product, reported to fail the USP dissolution test (7), has been evalu-

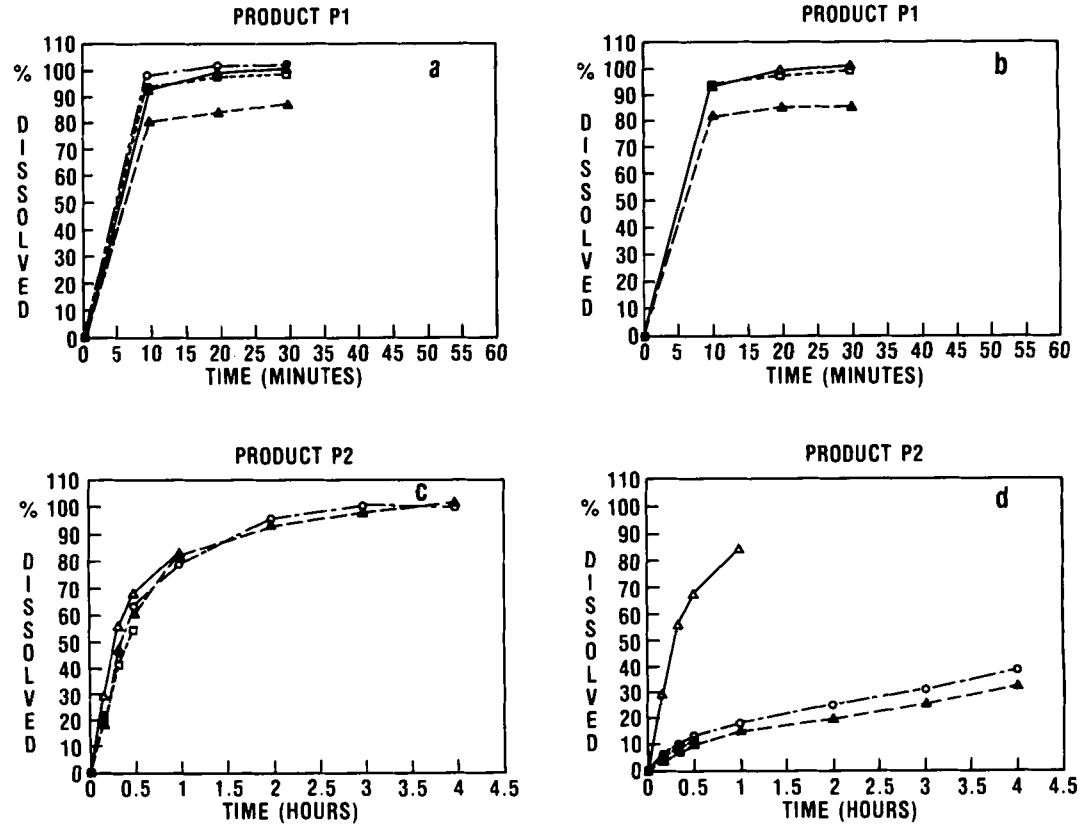

Figure 10—*Dissolution response of two lots of generic product P to 60% (a and c) and 75% (b and d) relative humidity aging for different time periods. Key: see Fig. 9.*

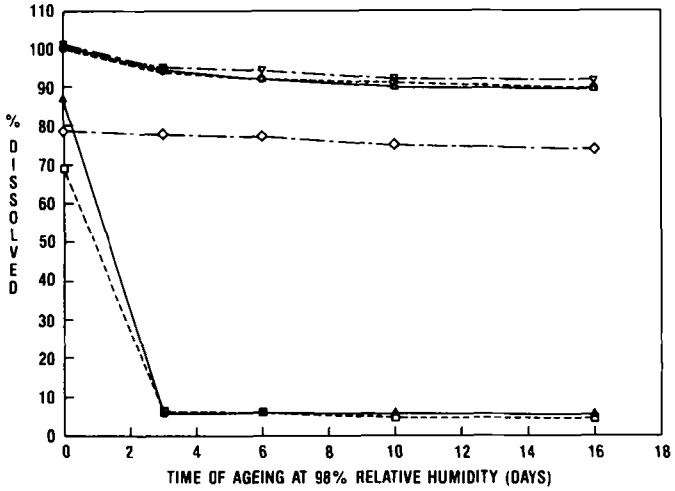

Figure 11—*Effect of short time aging on paddle-stirred dissolved drug at 30 min of different lots of U, P, and PH tolbutamide at 98% relative humidity. Key: (△) P1; (□) P2; (▲) P3; (◇) PH; (○) U1; (▽) U2.*

ated in 4 human subjects (13). The cause of the large *in vivo* variability in such a small study can not be precisely assigned. It may be due to product formulation and variable dissolution or subject variation. The variation observed *in vivo*, although larger for product P than U, was less than one might expect based on the USP dissolution test. That may be because the test does not simulate the normal exposure of tablets to the gastric acid of the stomach followed by exposure to intestinal fluid. Tuttle *et al.* (9) have reported that some tolbutamide tablets require exposure to an acidic environment in order to disintegrate and dissolve. It was proposed that these tablets contain inert formulation ingredients which are pH sensitive. Therefore, some tablets were pretreated in 0.1 M HCl for 30 min and then allowed to dissolve in pH 7.4 phosphate buffer using the USP paddle-stirrer test described in the *Experimental Section.*

Acid pretreatment produced a dramatic effect on dissolution time of P, but

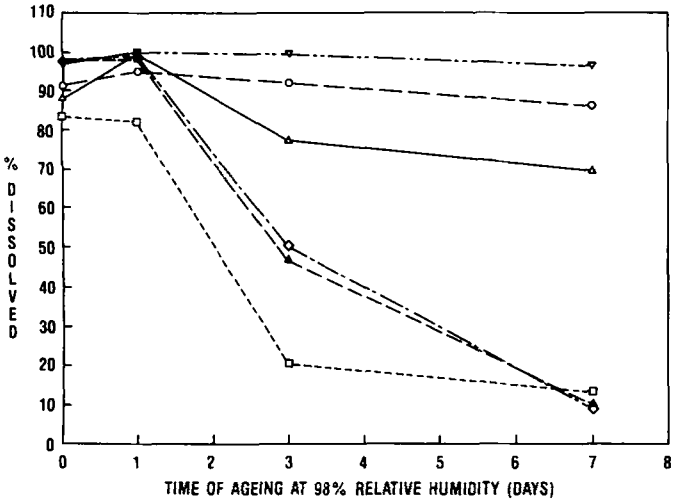

Figure 12—*Variation in paddle-stirred dissolved drug at 30 min of M, S, and Z after short-time aging at 98% relative humidity. Key: (△) M1; (□) M2; (◇) Z1; (▲) Z2; (○) S1; (▽) S2.*

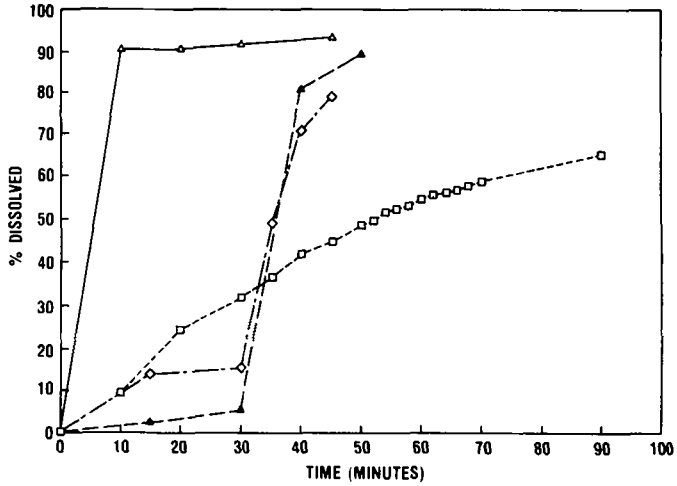

Figure 13—*Effect of pretreatment with simulated gastric fluid on U and P tolbutamide tablet products. The "no pretreatment" dissolution [(△)U; (□)P] was in phosphate buffer (pH 7.4) from time zero. The "acid pretreatment" dissolution [(◇)U; (▲)P] was in acid from time zero to 30 min and then in phosphate buffer from time 30 min to the last data point.*

had practically no effect on U (Fig. 13). That is, after acid pretreatment, both P and U dissolved at about the same rate as U without acid pretreatment. This dependence of the generic product on acid pretreatment may be undesirable (9).

Prolonged contact of tolbutamide with the GI tract, due to poor dissolution, may cause nausea, vomiting, or cramps (14). Constant patient monitoring appears prudent when products with highly variable interlot and intralot rates of dissolution are employed.

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