Acetaminophen III: Dissolution Studies of Commercial Tablets of Acetaminophen and Comparison with *In Vivo* Absorption Parameters

G. L. MATTOK, I. J. McGILVERAY, and C. A. MAINVILLE

Abstract □ Dissolution studies of eight different lots of acetaminophen tablets were investigated by means of three simple dissolution procedures. None of the methods provided complete correlation with physiological availability of acetaminophen when estimated from blood or urine profiles. Two lots of tablets, which were several years old, released the drug more slowly *in vitro* than more recently purchased lots of the same brands. All of the recently manufactured products required less than 15 min. for 50% dissolution; this time appears to be a reasonable limit for tablet formulations of acetaminophen.

Keyphrases □ Acetaminophen tablets—dissolution □ Absorption–dissolution parameters, comparison—acetaminophen □ Aging effects—acetaminophen tablet dissolution □ UV spectrophotometry—analysis

The design of an apparatus, suitable for the measurement of dissolution rates of solid dosage forms, is relatively straightforward. Hersey (1) commented recently that: "The number of dissolution rate methods described in the literature is almost equal to the number of workers in the field." However, there is a paucity of data comparing dissolution data from the various dissolution tests with quantitative *in vivo* availability results.

Levy (2) emphasized the need for *in vitro* tests that reflect faithfully dissolution rate-limited absorption of drugs from pharmaceutical dosage forms. A number of studies showed that dissolution characteristics of selected dosage forms of certain drugs (3–9), obtained using specific dissolution conditions, parallel blood or urine levels of the drug. However, no dissolution apparatus has been evaluated which would predict physiological availabilities of a variety of formulations of different drugs. [Many examples are cited in a recent bibliography by Wagner (10).]

In this study, eight lots of tablets, representing six brands of the moderately soluble drug acetaminophen, were examined with three simple dissolution tests. The dissolution times from the three tests with all the tablets were compared with physiological availability parameters obtained in 10 subjects in a separate study (11).

EXPERIMENTAL

Materials—Eight lots of tablets[1] (K_1, K_2, K_3, N, P, Q, R, and S) were used. The tablets, which had been evaluated in physiological availability studies, contained 300–500 mg. of acetaminophen according to label strength (11). Four newer lots (Q_2, Q_3, R_2, and R_3) and one other product (U) containing sorbitol were also studied.

Methods—Literature methods with some modifications were used. The resin kettle method (RK) differed from the original description (12) in that 900 ml. of dissolution fluid was used and the stirrer was centered in the jar so that the bottom of the shaft was 6.3 cm. from the bottom of the jar. The stationary basket method (SB) was similar to that described by Cook *et al.* (13), but for the present work the basket was constructed with a 30-mesh wire screen. The USP XVIII/NF XIII Method I or rotating basket method (14) was used with a stirring rate of 100 r.p.m. and 900 ml. dissolution fluid. Disintegration times were measured by an official method (15) using six tablets in simulated gastric and intestinal fluids.

Dissolution Fluids—Simulated gastric (0.1 *N* HCl) and intestinal (0.05 *M* phosphate buffer, pH 7.4) fluids were used.

Sample Assay—The same sampling procedure was used for the three methods. A 1-ml. Luer fitting tuberculin syringe, graduated in 0.01-ml. units, was attached to a medium-porosity glass filter by means of a female Luer joint (16). This device eliminated most particulate matter from the transfer of the sample to volumetric flasks. The sample (1.0 ml.) was diluted to 25 ml. with the dissolution fluid; its absorbance was measured at 243 nm. with a Beckman DU-2 spectrophotometer. The calibration curve for acetaminophen reference standard in gastric buffer is linear up to 25 mg./l.

Calculations—The label strength of each tablet was accepted. The concentration of each sample, corrected for the volume change caused by sample removal, was calculated from the calibration

[1] Letter indicates brand, number indicates different lots.

Table I—Dissolution Times of Acetaminophen Tablets in Gastric Buffer Using USP Method

Brand	Range[a], min.	t_{50}, min.	$\pm SD$	CV	T_{50}, min.
K_1	2.5–3.5	3.0	0.45	14.9	3.0
K_2	3–5	3.9	0.74	18.7	4.0
K_3	2–3.5	2.8	0.52	19.0	2.5
N	1.5–2.5	2.0	0.32	15.8	2.0
P	1.5–2.5	1.3	0.60	45.3	1.0
Q_1	16–22.6	20.2	3.47	17.2	20.0
R_1	14–29	20.2	6.71	33.2	18.5
S	1.0	1.0	0.00	0.0	1.0
Q_2	7.0, 6.5[b]	—	—	—	—
Q_3	5.0, 4.5[b]	—	—	—	—
R_2	4.0, 3.5[b]	—	—	—	—
R_3	1.5, 1.5[b]	—	—	—	—
U[c]	3.0, 3.0[b]	—	—	—	—

[a] Six-tablet test. [b] Two-tablet test. [c] Contained sorbitol.

Table II—Dissolution Times of Acetaminophen Tablets in Gastric Buffer Using RK Method

Brand	Range[a], min.	t_{50}, min.	$\pm SD$	CV	T_{50}, min.
K_1	3.5–13	5.3	2.81	53.6	4.5
K_2	2–11	4.9	2.80	57.7	3.5
K_3	3–12.5	7.7	3.82	49.9	6.0
N	2–3	2.6	0.39	15.2	3.0
P	0.5–1	0.95	0.16	16.6	1.0
Q_1	23–37	30.3	4.6	15.2	30.0
R_1	23.5–39	31.5	4.7	14.8	30.5
S	1.0	1.0	0.00	0.0	1.0
Q_2	5.5, 4.0[b]	—	—	—	—
Q_3	14.5, 12.0[b]	—	—	—	—
R_2	3.0, 3.0[b]	—	—	—	—
R_3	2.0, 2.0[b]	—	—	—	—
U[c]	4.5, 4.0[b]	—	—	—	—

[a] Ten-tablet test. [b] Two-tablet test. [c] Contained sorbitol.

Table III—Individual Dissolution Times (t_{50}) for Acetaminophen Tablets

Brand	t_{50}, min., in: Gastric Buffer SB Method	Intestinal Buffer SB Method	Intestinal Buffer RK Method
K_1	5.5, 5.0	6.0, 3.0	7.5, 4.0
K_2	5.0, 5.5	7.5, 14.0	8.5, 14.5
K_3	7.0, 6.0	9.5, 16.0	8.0, 25.0
N	7.0, 5.5	4.5, 3.0	2.0, 2.0
P	5.0, 4.0	2.0, 1.0	1.0, 1.0
Q_1	36.0, 35.0	105, 106	110, 126
R_1	32.0, 21.0	24.0, 27.0	15.0, 28.0
S	5.0, 5.0	1.0, 3.0	1.0, 0.5
Q_2	21.5, 18.5	76 , 69	
Q_3	13.5, 13.5	8.0, 14.0	
R_2	5.0, 5.0	6.5, 7.5	
R_3	5.0, 4.0	8 , 4.5	
U[a]	5.0, 6.5	6.0, 4.0	

[a] Contained sorbitol.

curve. The t_{50} values (or times for 50% of the labeled drug content to pass into solution) were obtained from a semilog plot of the percent undissolved drug against time. Mean t_{50} values, *i.e.*, $\bar{t}_{50}$, based on measurements with 10 tablets (RK method) or six tablets (USP/NF method), standard deviations, and coefficients of variation were then calculated. A plot of the average percent undissolved for 10 (RK method) or six (USP/NF method) tablets against sampling time provides a "mean dissolution rate curve" from which T_{50} was estimated. Dissolution measurements with the SB method were carried out on two tablets.

Physiological Availability—The protocol and regimen for the administration of the eight lots of acetaminophen tablets to 10 volunteers were described (11, 17). Blood samples collected at 20 and 40 min. and 1, 1.5, 2, 4, and 6 hr. after ingestion provided data for the estimation of the area under the free drug blood level curve (corrected to the same dose) for each tablet. Similarly, urine was collected at 1, 1.5, 2, 2.5, 3, 4, 5, 8, 11, 14, and 24 hr.; the mean availability of each dosage form was obtained from the total urinary excretion.

RESULTS

Dissolution—Dissolution characteristics of the original eight lots of acetaminophen tablets and five more recent lots are summarized in Tables I, II, and III. A typical set of curves used for calculating T_{50} values is shown in Fig. 1. Dissolution profiles for Q_1 with the RK method are compared in intestinal and gastric buffers in Fig. 2.

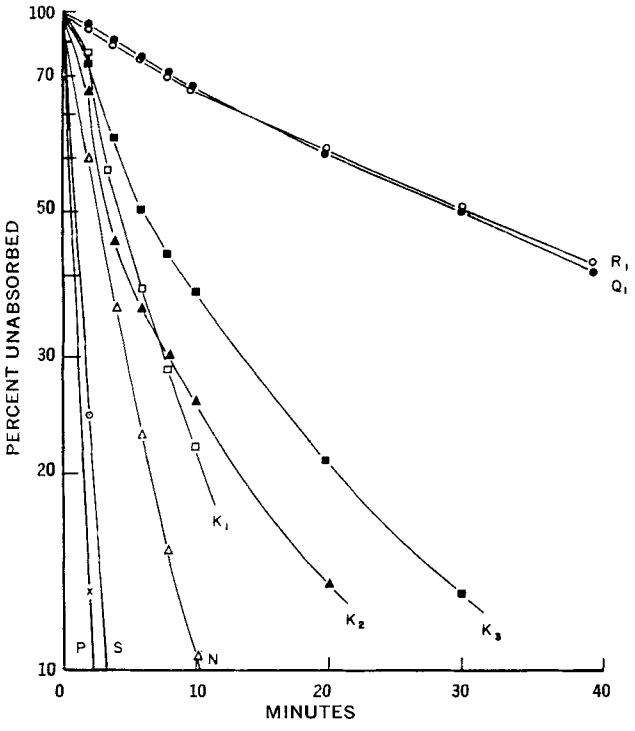

Figure 1—*Acetaminophen tablets. Curves for derivation of* T_{50} *in gastric buffer using RK method.*

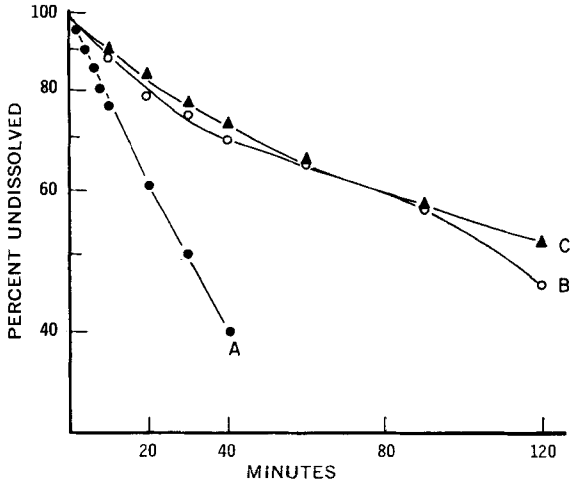

Figure 2—*Dissolution rate profiles with RK method for acetaminophen formulation* Q_1. *Key: A, average values* (±SD) *for 10 tablets in gastric buffer; B and C, individual tablets in intestinal buffer.*

Disintegration—Disintegration times of six tablets from lots K_1, Q_1, Q_2, Q_3, and R_1 in simulated gastric and intestinal buffers are shown in Table IV.

Physiological Availability—The results of a physiological availability study of acetaminophen dosage forms were fully described previously (11) and are summarized in Table V.

DISCUSSION

Comparison of Brands—Most of the acetaminophen tablets examined had $\bar{t}_{50}$ and T_{50} values in gastric buffer of less than 10 min. with the RK and USP/NF methods (Tables I and II). This limit was also indicated by single-tablet t_{50} values obtained with the SB method where two tablets of each lot number were tested (Table III). In the original group of eight lot numbers, brands Q_1 and R_1 were outstanding. These products had dissolution half-lives ($\bar{t}_{50}$ or T_{50}) more than twice as long as the other formulations in all the tests used. Since the formulations of these products were not known, only speculations can be made concerning the longer dissolution times. These differences in dissolution properties (Tables I–III) cannot be attributed to disintegration characteristics since disintegration times (Table IV) of Q_1 and R_1 in gastric buffer were comparable to those of K. However, it was known that these two samples had been on the shelf for about 3 years and they could thus have been "aged" compared to the others.

To establish whether more recently prepared lots of the same br nds would give altered dissolution characteristics, two tablet screening tests were done on two other lots of brands Q and R where the sequence of ages was $Q_1 > Q_2 > Q_3$ and $R_1 > R_2$ and R_3. The results are presented at the foot of Tables I, II, and III. Although there was apparently some interlot variation, the newer lots were closer to the other brands in dissolution behavior; in the Q series,

Table IV—Disintegration Times of Acetaminophen Tablets

Brand	Dissolution Medium	Range[a], min.	Mean[a], min.
K_1	Gastric	3–10	6
Q_1	Gastric	3–4	3
Q_2	Gastric	1–2	1
Q_3	Gastric	1.0	1
R_1	Gastric	1.5–2	2
K_1	Intestinal	3.5–4	4
Q_1	Intestinal	29–36	33
Q_2	Intestinal	28–38	31
Q_3	Intestinal	4–9	6
R_1	Intestinal	0.5–1	1

[a] Six tablets.

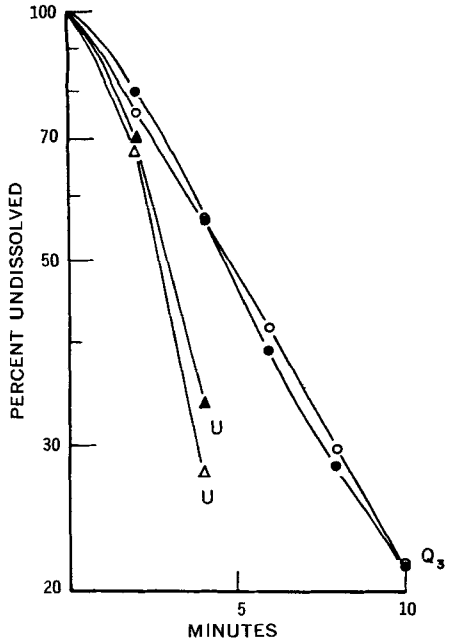

Figure 3—*Acetaminophen formulations Q_3 and U (with sorbitol). Individual curves for two tablets in gastric buffer using USP XVIII/NF XIII method.*

dissolution time increased with the age of the product. These findings suggest that either the formulations were changed to shorten the dissolution times or that the dissolution times of these formulations had increased with age.

A similar gradation in dissolution time in intestinal buffer was also observed (Table III). The dissolution half-life (t_{50}) of Q_1 increased three- to fourfold, and the mean disintegration time increased from 3 to 33 min. when the tests were done in intestinal buffer. Similar increases in t_{50} values were found for Q_2 and Q_3, t_{50} increasing with the age of the product, *i.e.*, $Q_1 > Q_2 > Q_3$. Furthermore, whereas dissolution of Q_1 in gastric buffer in the RK apparatus followed a regular exponential curve, first-order dissolution did not occur in intestinal fluid (Fig. 2). This was probably due to the poor disintegration properties of Q_1 in intestinal fluid which may

Table V—Physiological Availabilities from Blood Levels of Free Drug (PAB) and Urinary Excretion (PAU) of Acetaminophen Dosage Forms

Formulation	PAB, %	PAU, %
K_1	92.4	88.9
K_2	85.1	89.8
K_3	78.4	85.3
N	87.3	90.7
P	102.7	97.7
Q_1	91.8	89.3
R_1	98.9	92.9
S	97.1	88.1
T (control)	100.0	100.0

have resulted from aging. It was not due to a change in the intrinsic dissolution characteristics of acetaminophen at this concentration, since all the other formulations could be expected to be affected in a similar manner by the change of medium.

Tablets from three lot numbers of formulations K showed modest increases in t_{50} when the dissolution medium was changed from gastric to intestinal buffer in the SB method (Table III). However, the mean disintegration times for K_1 in intestinal fluid (4 min.) was somewhat less than in gastric buffer (6 min.). The increased t_{50} values in intestinal fluid must, therefore, be attributed to formulation rather than aging.

Formulation U, a commercial acetaminophen tablet, has a base containing sorbitol which is reported to improve the absorption of the drug (18). The dissolution half-lives of these tablets with any of the three methods were unremarkable compared to the normal group. These results are in contrast to the findings of Walters (19) who reported differences in $t_{0.9}$ (or $t_{90\%}$)—the time for solution of 90% of the drug—when two commercial formulations of acetaminophen were compared with another containing sorbitol. Since the dissolution apparatus used by Walters (19) was different from any of the three used in this study, any comparison with his results must be made with caution. Walters (19) found that the sorbitol-containing preparation gave t_{50} values of 3–4 min. However, dissolution times for U were close to those for all other brands examined except the "aged" formulations Q_1 and R_1 (Table I). Furthermore, the dissolution rate curve (Fig. 3) is similar to that of many other brands.

Comparison of Dissolution Methods—On the basis of the results of the present investigation, a comparison can be made of the RK and USP/NF dissolution methods with gastric fluid as the dissolu-

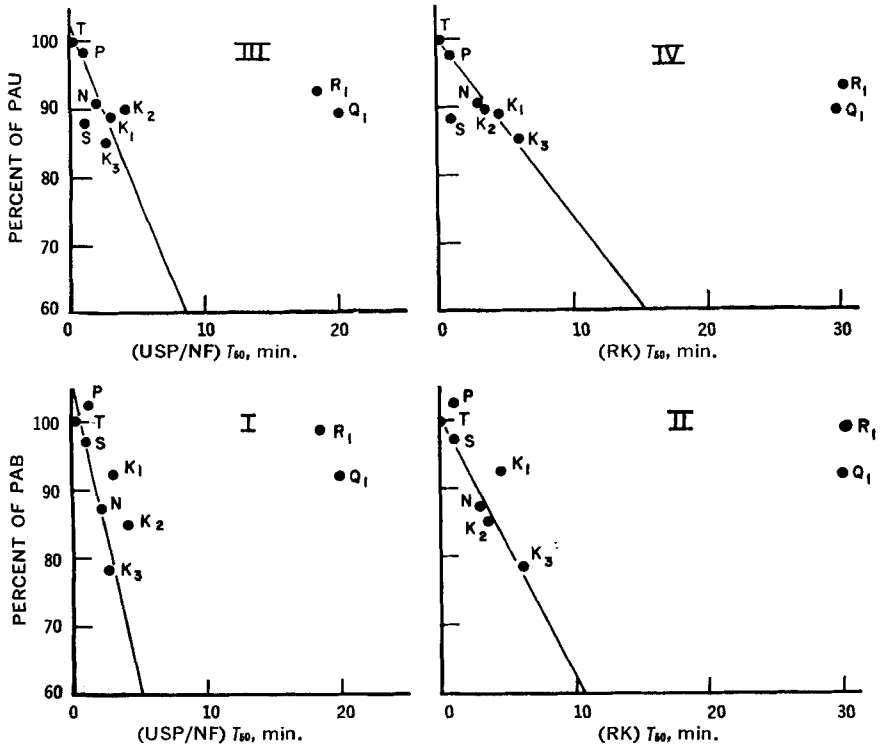

Figure 4—*Acetaminophen dosage forms. Plot of physiological availabilities (PA) from blood levels (I and II) and total urinary excretion (III and IV) against dissolution half-lives (T_{50}) in gastric buffer.*

tion medium. Rankings of the various formulations according to their $\bar{t}_{50}$ and T_{50} values are similar for both methods. Brands S and P release acetaminophen very rapidly, with T_{50} less than 1 min., while Q_1 and R_1 are the slowest to dissolve. These slower dissolving brands reverse their order of ranking (based on T_{50} values) in the two methods. This is attributed to intertablet variation, since the spread of individual t_{50} values is quite wide.

The most serious difference in the order of ranking and magnitude of values occurs with K_3, where $\bar{t}_{50}$ moves from 2.8 to 7.7 min. and T_{50} from 2.5 to 6.0 min. in the USP/NF and RK methods, respectively. The SB method shows a longer individual t_{50} value (6–7 min.) for K_3 compared to the USP/NF method. Individual tablet results for all lots of K indicate that the RK method is more sensitive to tablet variation than the USP/NF method. This is reflected in the coefficients of variation which are in the range 15–19 for the USP/NF method (Table I) and 50–58 for the RK method (Table II).

Individual tablet variation was also evident from the $\bar{t}_{50}$ values obtained with the SB and RK methods using intestinal buffer. The intertablet variations appear to be real, rather than artefacts of the RK system, since some other formulations tested showed similar coefficients of variation in both USP/NF and RK methods. In only two cases, P and R, was the USP/NF method more sensitive, based on coefficients of variation, than the RK method (Tables I and II). However, in the case of P the difference is exaggerated since t_{50} is low and the rate of dissolution is too rapid to derive a well-defined dissolution curve.

The USP/NF method gave shorter dissolution half-lives than the RK method for all brands except P and S which dissolved extremely rapidly, and discrimination was beyond the sensitivity of these intermittent sampling methods. This was to be expected (20) in view of the increased agitation in the USP/NF system. In addition to the increased stirring rate (100 *versus* 60 r.p.m.) used in the USP/NF method, the rotating basket of the USP/NF apparatus has a slight abrading effect on a tablet surface whereas the RK method depends only on liquid turbulence. Both USP/NF and RK methods appear to give an adequate assessment of acetaminophen tablet formulations for the purpose of a control laboratory. With brand K, where more than one lot was sampled, the RK method gave larger interlot and intralot variations and for this formulation it was the more discriminating method. The two-tablet tests done with Q_2 and Q_3 indicate that this conclusion may also be valid for formulation Q.

Comparison of Physiological Availability with Dissolution Data—Several authors have presented dissolution and absorption or physiological availability data on a few formulations of the same drug without attempting a direct correlation, *e.g.*, phenylbutazone (5), tolbutamide (8), and sulfisoxazole (7). Any correlation of availability–dissolution properties assumes that dissolution is the rate-limiting step in the absorption process. Most correlations which have been attempted were done with very few dosage forms and, even then, the correlation did not embrace all the dosage forms. Middleton *et al.* (21) were among the first to attempt to establish such a relationship. They plotted percent availability (from urinary excretion data) against disintegration and dissolution times (T_{50}). These results were used to demonstrate the increased predictive value of dissolution characteristics over disintegration in assessing the physiological availabilities of formulations. When this graphical method was applied to the acetaminophen dosage forms and the control solution (T), which was considered to have T_{50} of zero, most points were grouped close together except for the two older dosage forms, Q_1 and R_1, which had longer dissolution times (Fig. 4). With this type of curve, since there is no significant difference in availabilities (11), the availabilities of the different dosage forms should tend to the same value; therefore, the dissolution tests were more sensitive to changes in formulation than the biological tests. Any effect that the slower dissolution times of tablets Q_1 and R_1 may have had on the total absorption of acetaminophen must be hidden in the other variables of the trial.

A more sophisticated correlation of dissolution and absorption of drugs was introduced by Levy and his coworkers (22, 23). The rate of absorption of each dosage form was calculated and compared directly with the dissolution rate. The assumption was made that the kinetic model fitting the drug absorption process would usually also apply to the *in vivo* dissolution process when the absorption rate is dissolution rate-limited. It was further assumed that *in vitro* dissolution parallels *in vivo* dissolution. Thus, if percent dissolved *in vitro* is multiplied by a factor equal to the ratio of the first-order rate constants for *in vivo* absorption and *in vitro* dissolution and plotted against percent absorbed *in vivo* at the same time, a straight line of slope unity is obtained (23). With the present results, subject variations in the *in vivo* data prevented calculation of meaningful absorption rates by the Wagner–Nelson method (24) for each dosage form. Studies of these variations in acetaminophen metabolism are currently underway. For the same reason, the correlation of Cressman *et al.* (9) was inapplicable.

The dissolution rates of the acetaminophen tablets in this study provided T_{50} values varying from 1 to 30 min. with the RK method and from 1 to 20 min. with the USP/NF method. These differences in dissolution rates were not reflected in the physiologic availability. The more recently produced lots of tablets gave dissolution T_{50} values with either the USP/NF or RK method of under 15 min., and this would be a reasonable maximum value to propose for tablet formulations of this drug. (For the USP/NF method, a 10-min. maximum would appear to suffice.) The effect of tablet aging on tablet dissolution rate deserves further study.

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