triazines, however, alpha cleavage in accordance with Scheme I is not insignificant. Thus, XIV–XVII, whose methyl substituent may be expected to have only a mild inductive effect, yield ions derived from alpha cleavage, with an abundance second only to that of the base peak.

The GC behavior of the *s*-triazines is good. They elute at moderate temperatures and give essentially symmetrical peaks. The Kováts retention indexes (Table IV) were obtained by computation of the appropriate logarithmic data (18). Independent determinations were also made by use of the Hupe (19) diagram. On the average, results by both methods differed by less than 0.05%.

The conversion of biguanides into substituted *s*-triazines was used for the development of GC and mass fragmentographic methods for assaying phenformin in biological fluids. This treatment permitted the determination of plasma and saliva drug concentration–time profiles and of urinary drug excretion rates following a 100-mg oral dose of phenformin to human volunteers (20). A similar assaying approach is applicable for buformin and metformin. A detailed description of the analytical methodology and its limitations will follow in a separate publication.

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Correlation between Dissolution Characteristics and Absorption of Methaqualone from Solid Dosage Forms

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Abstract □ A methaqualone tablet in two strengths, 150 and 300 mg, was developed. The dissolution rate of an experimental formulation in pH 7.0 phosphate buffer, measured by the resin flask method, was shown to correlate with bioavailability in humans. The dissolution rate criterion was used to develop the final tablet formulation. Bioavailability of this formulation in two strengths was compared with a commercial capsule formulation and a slowly dissolving tablet formulation. Correlation between dissolution rate and bioavailability was shown in freshly prepared methaqualone tablet formulations. Bioavailability of tablets under accelerated stability testing conditions remained unaltered, whereas the dissolution rates in pH 7 phosphate buffer decreased, using the resin flask method. A rotating-flask method was developed, and dissolution in 0.1 *N* HCl at 2 rpm correlated with the bioavailability of both new and aged tablet formulations.

Keyphrases □ Methaqualone—solid dosage forms, dissolution rate correlated with bioavailability □ Dosage forms, solid—dissolution of methaqualone tablets correlated with bioavailability □ Dissolution—methaqualone tablets, correlated with bioavailability □ Bioavailability—methaqualone, correlated with dissolution of tablets

Methaqualone [2-methyl-3-(2-methylphenyl)-4-(3*H*)-quinazolinone] is a sedative–hypnotic and anticonvulsant compound of the 4-quinazolinone series (1). It is usually administered in tablet or capsule form, containing 150–300 mg of the base or hydrochloride salt. The pKa of the conjugate acid is 2.54, and its solubility is 0.3 mg/ml in water (2).

Peak serum levels have been observed within 2 hr after oral administration of methaqualone tablets (3). Other reports (4–6) also indicated the rapid absorption of methaqualone administered in various capsule and tablet formulations. Similar peak levels of methaqualone, within 2 hr, were reported for methaqualone–diphenhydramine hydrochloride tablets and capsules (7). Plasma and urinary excretion data were typical of a dissolution rate-limited process using 2-^{14}C-methaqualone capsules or tablets (4).

The effects of formulation variables on the dissolution of methaqualone were studied (8) in 0.1 *N* HCl, using Levy's beaker method (9); it was concluded

that no one technique or dissolution apparatus simulated *in vivo* conditions of methaqualone release from various tablet formulations. A relationship was shown between peak plasma levels of methaqualone in human subjects and the dissolution rates of tablets and capsules in pH 2 buffer (10).

The objective of this study was to develop a suitable *in vitro* dissolution technique that correlates with the bioavailability of newly prepared and aged methaqualone formulations.

EXPERIMENTAL

Dissolution Studies—*Resin Flask Method*—The procedure described by Poole (11) was modified to contain six separate stirring units chain driven by a common motor. Commercially available dissolution equipment[1] with a 5.1-cm (2-in.) stainless steel three-blade propeller[2] mounted on a stainless steel stirring shaft[3] was used. Stirrer speed was varied between 50 and 100 rpm. The volume of the dissolution medium was varied between 600 and 900 ml. Sampling of the medium and absorbance measurements were initially carried out manually but were later automated.

For the manual operation, samples (1.0 ml) of the dissolution fluid were removed at appropriate times by aspirating the fluid through a medium-grade, sintered-glass, gas dispersion tube into a pipet. The sample was diluted with 0.1 *N* NaOH, and the absorbance was determined at 236 nm.

For the automated operation, a medium-grade, sintered-glass, filter candle[4] was used as a filter. A peristaltic pump[5] was used to remove the dissolution medium simultaneously from three resin flasks, to filter and pump the filtrate into three flow-through cells[6], and then to return it to the resin flask; 600 and 900 ml of 0.1 *M* phosphate buffer (pH 7) were used for 150- and 300-mg methaqualone tablets, respectively.

All analyses were performed in triplicate. The absorbance of each sample was measured[7] and recorded[8] automatically with the aid of preset timers[9]. The absorbance was measured at 315 and 317 nm for the 150- and 300-mg methaqualone tablets, respectively. These wavelengths, rather than 236 nm (λ_{max}), were used since dilution of the sample for a reading at 236 nm would preclude recirculation of the sample in this closed system.

Rotating-Flask Method—The method described by Weintraub and Gibaldi (12) was used with a slight modification in the apparatus and with a dissolution medium volume of 600 ml of 0.1 *N* HCl. The rotation speed of the flask was varied between 0.5 and 6.0 rpm.

Accelerated Stability Testing—Tablets were stored at 40, 50, 60, 70, and 80° in closed containers. Unpackaged tablets were stored at room temperature and also at 40° in 80% relative humidity. Tablets packaged in blister packs were stored in 80% relative humidity. Tablets packaged in closed containers were stored in a light-temperature cycle cabinet (12 hr at 5° and 12 hr at 45°).

Formulations Studied—Table I lists the dosage form and the amount of methaqualone base or hydrochloride salt in the various formulations used.

Bioavailability Studies—All bioavailability studies were conducted in accordance with previously described procedures in normal fasted subjects (4). A 4 × 4 Latin-square design with three replications was used for Formulations A–D in 12 subjects. A 6 × 6 Latin-square design was used for Formulations P–U in six subjects. A completely randomized block design was used for Formulations C and K–N in three subjects.

Serum methaqualone levels were measured by a modification of the spectrofluorometric procedure of Brown and Smart (13). All data were subjected to an analysis of variance for the particular statistical design.

Table I—Formulations Used

Formulation	Dosage Form	Methaqualone: Chemical Form[a]	Methaqualone: Strength, mg
A	Tablet	Base	150
B	Tablet	Base	300
C	Tablet	Base	300
D	Capsule	Salt	200
P	Tablet	Base	300
Q	Capsule	Base	300
R	Tablet	Base	300
S	Tablet	Base	300
T	Tablet	Base	300
U	Capsule	Salt	200
K	Tablet	Base	150
L	Tablet	Base	150
M	Tablet	Base	150
N	Tablet	Base	150

[a] Methaqualone base is listed as base, and methaqualone hydrochloride salt is listed as salt.

RESULTS AND DISCUSSION

Preliminary dissolution studies using the resin flask technique with several methaqualone formulations in 0.1 and 0.01 *N* HCl showed no correlation between dissolution and bioavailability profiles. However, dissolution studies in phosphate buffer (pH 7) did show dissolution profiles that correlated with bioavailability data.

The dissolution in phosphate buffer, using the resin flask technique, was studied with Formulations A–D (Table II). The dissolution of 150-mg methaqualone tablets was studied in 600 ml of pH 7 phosphate buffer stirred at 60 rpm, and the dissolution of 300-mg tablets was studied in 900 ml of pH 7 phosphate buffer at 90 rpm. The rates of dissolution were equivalent at the different stirring speeds as shown by dissolving two 150-mg tablets in 900 ml of medium at 90 rpm.

The reproducibility of the dissolution procedure was confirmed with three sets of tablets from two lots of 300-mg tablets and one lot of 150-mg tablets. Three sets of capsules, from one lot of commercially marketed capsules containing 200 mg of methaqualone hydrochloride, were also studied for dissolution characteristics. The reproducibility of the dissolution analysis, as indicated by the standard deviation, was acceptable with all tablet formulations. However, the variation with the capsule formulation was much greater than with tablets.

This variation could be attributed to the difference in the mode of disintegration of tablets and capsules prior to dissolution. Tablets disintegrated immediately, and the methaqualone was instantly available for dissolution purposes. However, the dissolution characteristics of the capsule shell and physical interaction of the partially dissolved, solvated gelatin with the capsule contents introduced a variable time lag in the dissolution profile. Since the extent to which the gelatin hampered the dissolution differed from capsule to capsule, the variability in dissolution data for capsules was greater than that for tablets.

A 300-mg methaqualone formulation was developed in both capsule and tablet dosage forms. The dissolution profiles of these two formulations (P and Q) and four other formulations in pH 7 phosphate buffer are shown in Fig. 1. Tablet Formulations R and S were identical except that the methaqualone used was obtained from two different manufacturers. Formulations T and U were commercially available formulations in the forms of a tablet and a capsule containing 300 mg of methaqualone base and 200 mg of methaqualone hydrochloride, respectively.

The similarity in dissolution profiles of Formulations P, Q, T, and U is apparent. These profiles differ considerably from those of Formulations R and S. The bioavailability of these formulations was determined in six subjects. The average serum concentration profiles of methaqualone are shown in Fig. 1. The mean methaqualone serum concentrations at 0.5, 1, 2, and 3 hr of Formulations P, Q, T, and U are statistically equivalent and significantly different from Formulations R and S. Area under the curve (*AUC*) measure-

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[7] Model 210, Gilford Instrument Laboratories, Oberlin, Ohio.
[8] Leeds & Northrop, North Wales, Pa.
[9] Industrial Timer Corp., Parsippany, N.J.

Table II—Dissolution Profiles of Various Methaqualone Formulations[a]

Minutes	Methaqualone in Solution, $\bar{X}$ % ± SD				
	Formulation A[b]	Formulation A[c]	Formulation B[c]	Formulation C[c]	Formulation D[b]
10	63.2 ± 3.4	65.7 ± 2.0	57.9 ± 5.1	17.8 ± 2.7	18.0 ± 6.7
20	84.1 ± 2.2	80.5 ± 3.7	77.2 ± 4.0	29.6 ± 2.7	49.9 ± 8.8
30	92.5 ± 1.7	86.5 ± 4.5	85.3 ± 3.2	36.6 ± 2.8	71.4 ± 13.3
40	96.4 ± 1.5	89.7 ± 4.9	89.4 ± 2.8	41.6 ± 2.7	81.8 ± 13.2
50	98.2 ± 1.4	91.8 ± 5.2	92.1 ± 2.4	45.6 ± 2.6	87.2 ± 12.0
60	99.6 ± 1.4	92.8 ± 5.0	93.6 ± 2.1	48.8 ± 2.4	91.2 ± 11.3

[a] Dissolution was studied using the resin flask procedure with phosphate buffer (pH 7). Formulation A = 150-mg methaqualone tablet, Formulation B or C = 300-mg methaqualone tablet, and Formulation D = 200-mg methaqualone hydrochloride capsule. [b] Dissolution of one tablet (A) or one capsule (D) in 600 ml of buffer at 60 rpm. [c] Dissolution of two 150-mg tablets (A) or one 300-mg tablet (B or C) in 900 ml of buffer at 90 rpm.

Table III—Correlation of Dissolution and Area under the Serum Concentration Curve (*AUC*) with Various Formulations

AUC, μg hr/ml	Correlation Coefficient[a]					
	Dissolution Sampling Time, min					
	10	20	30	40	50	60
0–3	0.811[b]	0.979[c]	0.988[c]	0.987[c]	0.989[c]	0.990[c]
0–6	0.874[b]	0.986[c]	0.990[c]	0.985[c]	0.984[c]	0.987[c]

[a] Regression analysis of percent methaqualone in solution *versus* area under the curve with Formulations P-U. [b] Statistically significant, $p < 0.05$. [c] Statistically significant, $p < 0.001$.

ments at all testing intervals, *e.g.*, 0–0.5, 0–1, and 0–2 hr, confirmed these conclusions.

Formulations P, Q, T, and U dissolved very rapidly and reached a dissolution plateau of 95% in 30 min; they were rapidly absorbed and achieved equivalent peak serum concentrations within 1 hr. Formulations R and S, which dissolved slowly, did not reach 100% dissolution even after 60 min. These tablets were poorly absorbed and had lower serum levels throughout the experiment. The dissolution data obtained with Capsule U showed a lag period, consistent with the previous explanation for slower dissolution with capsule formulations.

Regression analysis of the serum *AUC* at 0 → 3 and 0 → 6 hr of Formulations P–U *versus* percent methaqualone in solution at 10, 20, 30, 40, 50, and 60 min indicated a highly significant correlation (Table III).

Subsequent studies resulted in the development of tablet Formulations A and B, containing 150 and 300 mg of methaqualone, respectively. The bioavailability of these formulations was compared to a slowly dissolving formulation (C) and a commercially available capsule formulation of methaqualone hydrochloride (D). There was no significant difference between the mean methaqualone serum concentrations at all sampling times for Formulations A, B, and D (Fig. 2). Peak serum concentrations of all four formulations were observed in 1–1.5 hr.

In this bioavailability experiment, the dose of methaqualone hydrochloride in Formulation D (349 mg of methaqualone base) was higher than in Formulations A and B; the peak serum concentrations were statistically equivalent. When the area under the curve for the 0–6-hr period for Formulation D was normalized to 300 mg of methaqualone base, the value obtained was 11.4 μg hr/ml as compared to 10.8 and 11.3 μg hr/ml for Formulations A and B, respectively.

The mean methaqualone serum concentrations and area under the curve of Formulation C were significantly lower than those of the other three formulations. The dissolution profiles in Fig. 2 predict that Formulation C should be lower in bioavailability than Formulations A, B, and D. When the lag time inherent in the dissolution profile of Capsule D is considered, the dissolution profiles

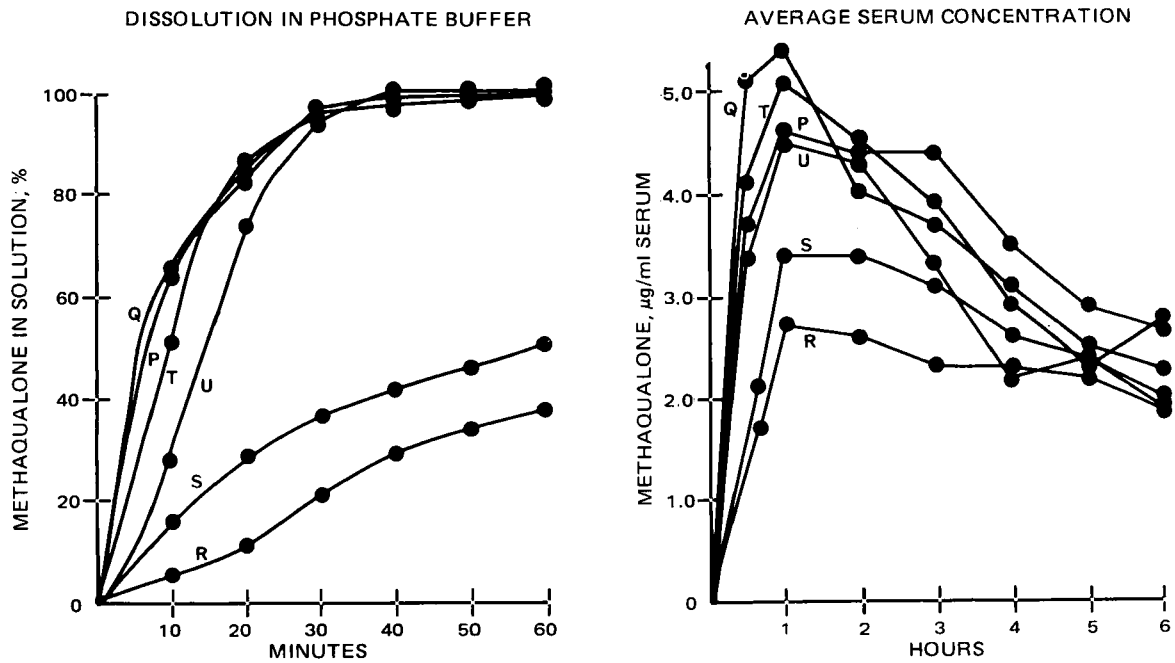

Figure 1—*Dissolution profiles measured by resin flask method for Formulations P–T in 900 ml of pH 7.0 phosphate buffer stirred at 90 rpm and for Formulation U in 600 ml of pH 7.0 phosphate buffer stirred at 60 rpm and average serum methaqualone levels for the formulations in six subjects with 600-mg dose.*

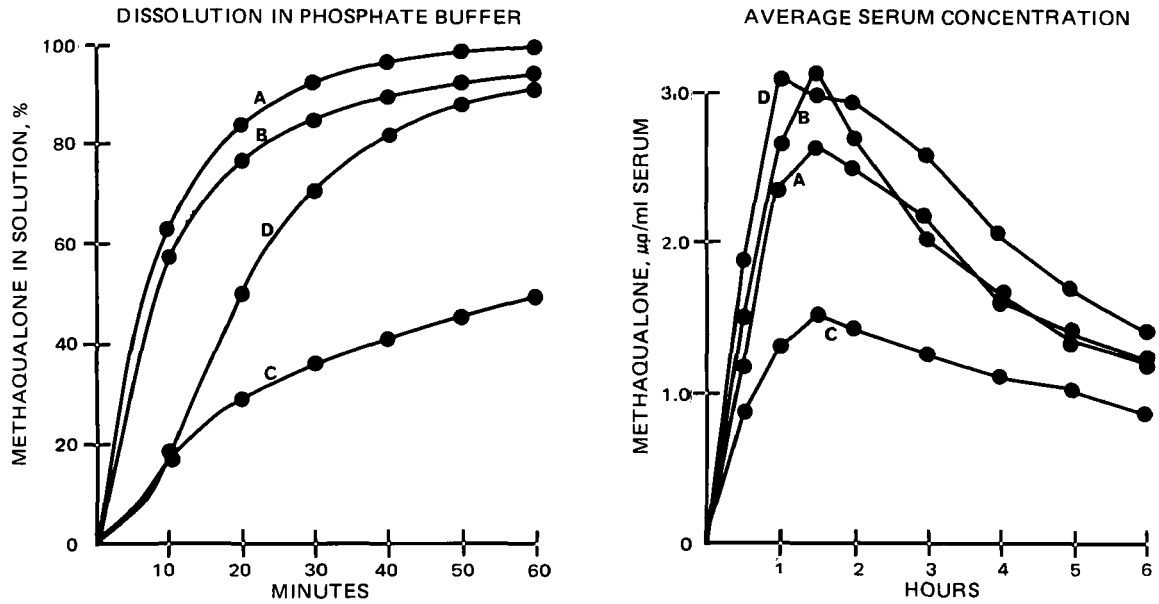

Figure 2—*Dissolution profiles measured by resin flask method for Formulations A, B, and D in 600 ml of pH 7.0 phosphate buffer stirred at 60 rpm and for Formulation C in 900 ml of pH 7.0 phosphate buffer stirred at 90 rpm and average serum methaqualone levels for the formulations in 12 subjects with 300-mg dose.*

for Formulations A, B, and D become similar. The dissolution profiles predicted that the bioavailability of 300 mg of methaqualone administered as one 300-mg tablet (Formulation B) or two 150-mg tablets (Formulation A) should be equivalent to each other and to capsule Formulation D.

Regression analyses of serum *AUC* 0 → 3 and *AUC* 0 → 6 *versus* percent dissolved in phosphate buffer are shown in Table IV. Statistically significant correlations were observed between percent dissolved in 40, 50, and 60 min and *AUC* 0 → 3 and 0 → 6 hr. Thus, the correlation previously established with the intermediate formulations (P–S) was observed with the final formulations (A and B). Equivalency in bioavailability of two strengths of a dosage form (150- and 300-mg tablets) was also demonstrated. This aspect is important and must be considered in the design and evaluation of drug products in various unit doses.

The final 150- and 300-mg methaqualone tablet formulations were tested for their chemical and physical stability by subjecting them to accelerated stability conditions, which included storing the tablets in open containers and subjecting them to high temperatures and high humidity. There was no change in the chemical stability of the methaqualone. The disintegration times of tablets stored at high temperatures increased slightly but never exceeded 10 min. The dissolution rates of tablets subjected to high humidity–high temperature conditions were considerably reduced (Table V).

Four different 150-mg methaqualone tablet formulations (K–N) with variable decreased dissolution rates were tested for their bioavailability in three subjects. The same three subjects were used throughout this phase of the study. The dissolution data and average serum methaqualone concentrations are shown in Table V.

Table IV—Correlation Coefficient of Percent Dissolved *versus* Area Under the Serum Level Curve (*AUC*) for Formulations A–D

AUC, μg hr/ml	Correlation Coefficient[a]					
	Dissolution Sampling Time, min					
	10	20	30	40	50	60
0–3	0.527	0.758	0.888	0.929[b]	0.943[b]	0.949[b]
0–6	0.500	0.747	0.890	0.937[b]	0.952[c]	0.960[c]

[a] Regression analysis of percent methaqualone in solution *versus* area under the curve with Formulations A–D. [b] Statistically significant, $p < 0.1$. [c] Statistically significant, $p < 0.05$.

The mean serum methaqualone concentrations of Formulations K–N were statistically equivalent. This finding is in contrast to their distinctly differing dissolution data. From the dissolution data, one would predict that Formulations M and N would be absorbed more slowly and to a lesser extent than Formulations K and L. Regression analysis showed no correlation between dissolution and bioavailability of aged samples.

The bioavailability of Formulation C, which had previously been demonstrated to have poor dissolution and poor bioavailability in a larger population, was also tested in these three subjects. Formulation C contained 300 mg of methaqualone. It was used as an intact tablet since cutting in half would tamper with the dosage form and change the surface characteristics. Table V lists the area under the curve for Formulation C, normalized to a 150-mg dose. Smyth *et al.* (4, 5) substantiated this normalization process. Normalization was carried out by halving the *AUC* for the 300-mg dose.

The serum levels in the three subjects for Formulation C were equivalent to those in a larger population. Thus, the data obtained with the other four formulations (K–N) were considered to be reflective of a larger population and clearly indicated that differing dissolution profiles of Formulations K–N in phosphate buffer did not correlate with their bioavailability in humans. When this discrepancy was observed between dissolution profiles using the resin flask method and the bioavailability data after administration of Formulation L, several other dissolution methods were investigated.

Dissolution rates were studied using the rotating-flask technique at speeds ranging from 0.5 to 6 rpm in 600 ml of 0.1 *N* HCl. Results obtained at 2 rpm and above were reproducible. Dissolution data obtained below 2 rpm showed differences between the formulations, which were not apparent in bioavailability. Dissolution studies by this method in pH 7.0 phosphate buffer also showed very poor correlation with bioavailability.

Dissolution data on Formulations L–N at 2 (Table VI) and 4 rpm were similar. Even though Formulation N was initially slow in dissolving, all three formulations released close to 100% of their contents into the dissolution medium after 40 min. Therefore, it appears that dissolution studies using the rotating-flask method may give the best correlation with bioavailability.

Bioavailability studies are usually conducted on freshly prepared formulations, because it is assumed that bioavailability will remain unaltered with age unless some physicochemical changes in the formulation are observed. However, little work has been reported on the correlation between dissolution rate and bioavailability of aged formulations. This report has shown that dissolution technology applied to freshly prepared formulations is not necessarily applicable to aged samples. Consequently, methods

Table V—Dissolution and Bioavailability Data on Stability Samples of Methaqualone Tablets

Time	Methaqualone in Solution, %[a]				
	Formulation K[b], 2 months at Room Temperature	Formulation L[b], 3 months in Light-Temperature Cycle	Formulation M[b], 7 months at 80% R.H. and Room Temperature	Formulation N[b], 8 months at 80% R.H. and 40°	Formulation C[b], 33 months at Room Temperature
0 min	0	0	0	0	0
10 min	53.7 ± 5.3	46.6 ± 2.7	18.2 ± 2.3	10.0 ± 1.6	3.3 ± 1.1
20 min	72.1 ± 6.3	67.8 ± 1.6	34.1 ± 4.4	18.2 ± 4.1	11.0 ± 0.6
30 min	81.0 ± 7.3	78.7 ± 0.6	45.9 ± 3.2	25.4 ± 6.2	16.6 ± 0.5
40 min	85.1 ± 7.0	84.4 ± 2.3	54.3 ± 4.2	31.4 ± 7.5	21.3 ± 1.0
50 min	87.7 ± 6.2	87.9 ± 1.4	60.1 ± 3.9	35.8 ± 8.4	25.9 ± 0.9
60 min	89.0 ± 5.2	90.5 ± 2.3	66.0 ± 4.2	39.8 ± 9.2	30.7 ± 0.6
	Serum Methaqualone, μg/ml[c]				
0 hr	0	0	0	0	0
0.5 hr	1.4 ± 0.3	1.5 ± 0.3	1.1 ± 0.5	1.3 ± 0.0	1.7 ± 0.2
1 hr	1.6 ± 0.3	1.9 ± 0.4	1.6 ± 0.2	1.7 ± 0.4	2.5 ± 0.5
1.5 hr	—	—	1.9 ± 0.6	2.3 ± 0.5	2.1 ± 0.6
2 hr	1.1 ± 0.1	1.4 ± 0.0	1.7 ± 0.6	1.4 ± 0.4	1.7 ± 0.3
3 hr	1.1 ± 0.2	1.1 ± 0.1	1.2 ± 0.3	0.8 ± 0.3	1.4 ± 0.3
4 hr	1.0 ± 0.2	0.8 ± 0.1	1.1 ± 0.4	0.6 ± 0.2	1.1 ± 0.2
5 hr	0.9 ± 0.3	0.7 ± 0.1	0.8 ± 0.2	0.5 ± 0.2	1.0 ± 0.3
6 hr	0.8 ± 0.1	0.7 ± 0.2	—	—	—
$AUC^{0-3\ hr}$, μg hr/ml	3.58	4.10	4.28	4.10	4.99 (2.49[d])
$AUC^{0-5\ hr}$, μg hr/ml	5.62	5.79	6.35	5.35	7.29 (3.65[d])

[a] Dissolution was measured using the resin flask method with phosphate buffer (pH 7). (See Table II for conditions.) Values are the average concentrations ± *SD*. [b] Formulations K-N = 150-mg methaqualone tablet identical to Formulation A but stored under various stability conditions, and Formulation C = 300-mg methaqualone tablet. (R.H. = relative humidity.) [c] Average data for bioavailability study in three subjects at a 150-mg methaqualone dose for Formulations K-N and at a 300-mg methaqualone dose for Formulation C ± *SD*. [d] Area under the curve normalized to 150-mg methaqualone dose.

Table VI—Dissolution of Methaqualone Tablets by the Rotating-Flask Method

Minutes	Methaqualone in Solution, %[a]			
	Formulation L[b]	Formulation M[b]	Formulation N[b]	Formulation C[b]
10	89.7 ± 7.3	88.9 ± 4.3	59.5 ± 6.0	27.9 ± 8.3
20	96.2 ± 5.4	96.2 ± 3.5	80.0 ± 6.1	45.5 ± 6.5
30	100 ± 3.2	100 ± 2.5	88.1 ± 4.9	58.1 ± 7.2
40[c]	—	—	92.2 ± 3.7	67.0 ± 3.2
50	—	—	94.9 ± 3.8	72.1 ± 4.9
60	—	—	96.3 ± 2.9	78.1 ± 6.8

[a] Using 600 ml of 0.1 *N* HCl at 37° in a 2-liter flask rotated at 2 rpm. Values are the average concentrations ± *SD*. [b] Formulations L-N = 150-mg methaqualone tablet identical to Formulation A but stored under various stability conditions, and Formulation C = 300-mg methaqualone tablet (see Table V). [c] Dissolution for Formulations L and M was stopped after 30 min.

that show correlation between dissolution characteristics and bioavailability of aged samples must be developed for each drug product.

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