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Dependence of Area under the Curve on Proquazone Particle Size and *In Vitro* Dissolution Rate

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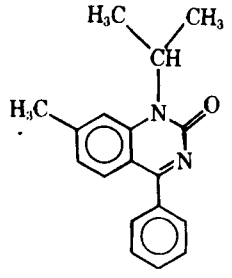
Abstract □ The *in vitro* dissolution and GI absorption of various sieve fractions of proquazone were studied (particle-size ranges of 45–74, 160–300, and 500–1000 μm). The dissolution rates of preparations F45, F160, and F500 were determined *in vitro* in a flow-through assembly in artificial gastric juice at 37°. The time required for 63% of the maximum amount of soluble drug to pass into solution was characterized by the dissolution variable τ_D. The *in vitro* dissolution rates for the preparations differed significantly in the order $\tau_{D,F45} < \tau_{D,F160} < \tau_{D,F500}$. After oral administration of 300 mg of the fractions to each of eight rhesus monkeys, the area under the plasma level–time curve (AUC) differed significantly in the order $AUC_{F45} > AUC_{F160} > AUC_{F500}$. The dissolution rate increased with decreasing particle size. The AUC increased with decreasing particle size and with increasing dissolution rate. These results indicate that the dissolution rate probably determines the extent of absorption when dissolution is rate limiting.

Keyphrases □ Proquazone—effect of particle size on area under the curve □ Dissolution rate, *in vitro*—proquazone, dependence on particle size □ Particle size—proquazone, effect on *in vitro* dissolution rate

After oral administration of solid dosage forms, absorption from the GI tract can be described as a sum of two consecutive transport processes: (*a*) dissolution of the drug from the dosage form (which produces a solution, micelles, or a solubilized entity), characterized by the dissolution rate constant k_1 for dissolution *in vivo;* and (*b*) transport of the drug to and through the intestinal membranes and its penetration into the general circulation, characterized by the total absorption rate constant k_2.

It is possible to distinguish between two fundamentally different cases (1): either the dissolution proceeds more slowly than the absorption ($k_1 < k_2$), or the absorption proceeds more slowly than the dissolution ($k_1 > k_2$). When $k_1 < k_2$, it should be possible to increase the absorption rate by increasing k_1 through a reduction in the particle size (2). When $k_1 > k_2$, a reduction in the particle size cannot affect the absorption rate.

The effect of particle size on relative absorbability has been demonstrated for several drugs, *e.g.*, griseofulvin (3), tetracycline (4), tolbutamide (5), and benoxaprofen (6). There also have been reviews on this subject (7–9). The relationship between particle surface area and GI absorption holds when absorption is dissolution rate limited, *i.e.*, when $k_1 < k_2$. For example, for proquazone, with a saturation solubility of 0.1% in artificial gastric juice, the area under the curve as a function of particle size and as a function of the *in vitro* dissolution rate was investigated. Proquazone[1] (I) is a quinazolidine anti-inflammatory drug.



I

EXPERIMENTAL

The experimental preparation was crystallized from ethyl acetate. A sonic sifter[2] followed by an air-jet sieve[3] was used to fractionate the product into the following ranges: 45–74 μm (F45), 160–300 μm (F160), and 500–1000 μm (F500). Care was taken to ensure that the particle-size ranges did not overlap. The experimental fractions were packed by hand in hard gelatin capsules for oral administration. The packing appeared to be very loose when the content was inspected.

The measurement of the dissolution rate was carried out in a flow-through assembly at a rate of 33 ml/min and at 37° (10). The solvent consisted of 0.082 *N* HCl and 0.034 *M* NaCl at pH 1.2. Samples were drawn after 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 180, and 240 min. The concentration of free drug was determined spectrophotometrically at 232 nm.

Male rhesus monkeys (*Macaca mulatta*), ~3 years old and 8–10 kg, received no food for a period extending from 20 hr before administration to 4 hr after it, but they had free access to water. A 300-mg proquazone

[1] Biarison, Sandoz Ltd.
[2] Allen Bradley, Fisher Scientific Co.
[3] Alpine, Augsburg, West Germany.

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Table I—*In Vitro* Dissolution Rate (Percent Dissolved) at a Given Time

Minutes	F45 Mean[a]	F45 SD[b]	F160 Mean	F160 SD	F500 Mean	F500 SD
5	8.6	4.4	4.2	1.2	2.5	0.6
10	43.1	2.9	13.1	1.4	6.8	0.7
15	68.6	4.1	21.9	2.0	10.8	0.7
20	81.5	4.0	30.5	2.2	14.9	1.1
25	85.5	3.7	38.3	2.0	18.9	1.3
30	88.6	3.2	45.4	2.5	22.9	1.5
45	93.2	2.4	61.9	2.2	33.0	1.9
60	95.6	2.3	73.9	1.8	46.9	10.2
90	97.6	2.0	88.2	1.3	60.7	8.5
120	97.7	2.7	94.8	1.0	68.5	2.6
180	97.6	2.3	98.7	0.6	83.8	1.8
240	96.7	2.6	99.2	1.0	91.7	2.3
τ_D, min[c]	8.5	1.2	42.8	2.9	93.1	9.8

[a] Three determinations. [b] Standard deviation. [c] Values for the time where 63% of the maximum amount of soluble drug passes into solution were obtained using the Weibull distribution. This distribution is a general linearization function that was described for dissolution rate curves (17). The τ_D values were estimated according to a plot that was obtained using the published empirical function (14) and, therefore, may not necessarily correspond to the experimental timing where 63% of the drug was dissolved.

capsule was administered to each animal orally by provoking a swallowing reflex with the finger. The capsule was rinsed down with 5 ml of tap water. Blood, 2.5 ml, was drawn at 0, 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 24 hr.

The fluorometric method detected the unchanged compound and the 7-hydroxymethyl metabolite in the plasma. The plasma concentration is expressed in nanogram equivalents of proquazone per milliliter. By the addition of 2 *N* sodium carbonate, the alkaline plasma sample (1 ml) was extracted into *n*-heptane. This sample was reextracted into 5 *N* aqueous HCl. The compound was excited at 326 nm, and its emission was measured at 510 nm.

For the *in vitro* dissolution experiments, the homogeneity of the mean values was tested by simple analysis of variance and the differences between mean values were tested by the Student–Newman–Keuls test (11).

The plan for the experiments in laboratory animals was arranged according to two independent random designs based on 4 × 4 Latin squares. Since another proquazone preparation had to be tested, it was included in the experimental design but was not evaluated further. The homogeneity of the mean values was tested by analysis of variance for repeated Latin squares (12), and the distinction between mean values was verified by Tukey's test (13).

RESULTS AND DISCUSSION

The experiments on the dissolution rate were evaluated by means of the dissolution variable τ_D (14). The τ_D value is the time in minutes during which 63% of the maximum amount of soluble drug passes into solution.

Table II—Mean Plasma Level Data[a] (Nanogram Equivalents per Milliliter) for Proquazone

Hours	F45 Mean	F45 SD[b]	F160 Mean	F160 SD	F500 Mean	F500 SD
0	0		0		0	
0.33	229	266	41	80	11	15
0.66	834	727	84	125	66	60
1	1191	798	106	146	83	61
1.5	1217	820	116	141	76	47
2	830	563	122	127	62	40
2.5	601	297	101	107	57	41
3	509	238	125	109	56	71
4	357	185	159	165	64	87
6	231	118	149	98	61	88
8	152	71	75	36	56	59
24	153	182	105	97	43	24
AUC[c]	6156	3159	1966	674	986	499

[a] Experiments were conducted in eight rhesus monkeys after oral gavage of various sieve fractions of the drug: F45 (45–74 μm), F160 (160–300 μm), and F500 (500–1000 μm). [b] Standard deviation. [c] The area under the plasma level–time curve (*AUC*) (nanogram equivalents per milliliter per hour) was estimated by an approximate integration formula, the trapezoidal rule.

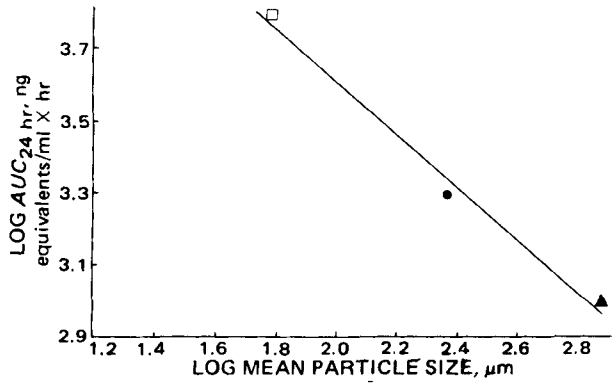

Figure 1—*Linear relationship between the logarithm of the mean value of the area under the plasma level–time curve* (AUC) *and the logarithm of the mean value of the particle size for preparations F45 (45–74 μm, □), F160 (160–300 μm, ●), and F500 (500–1000 μm, ▲).*

In the experiments in rhesus monkeys, three of the animals had to be replaced. The influence of the particular animal was negligible in comparison with the clearly significant effect of the product; *i.e.*, the variance component caused by the animals was about three times less than that caused by the product. Blood samples could only be obtained up to a maximum period of 24 hr because of sampling difficulties. Therefore, the area under the plasma concentration–time curve (*AUC*) was integrated up to 24 hr employing the trapezoidal rule.

The fluorometric analysis was carried out on plasma samples on the assumption that there was a constant distribution of the drug and metabolites between plasma and blood cells. From *in vitro* binding experiments using human blood, the quantity of drug and metabolites bound to blood cells was known to amount to ~20%. To comply with the conditions necessary for the analysis of variance, the figures for the *AUC* were submitted to a logarithmic transformation. Because of the small number of particle-size ranges investigated, no attempt was made to establish quantitative correlative equations. Nalimov's test was applied to the measurements to detect outliers before statistical analysis (15). Significant outliers ($p < 0.01$) were replaced by the next highest or the next lowest value (16).

Table I shows that the *in vitro* dissolution rate increased with decreasing particle size. The statistical analysis of the dissolution variable, τ_D, of preparations F45, F160, and F500 yielded the following significant series ($p = 0.01$): $\tau_{D,F45} < \tau_{D,F160} < \tau_{D,F500}$. By calculation, log τ_D for F45, F160, and F500 for the particle-size ranges investigated was a linear function of the logarithm of the mean particle size.

The mean plasma level–time profile (Table II) shows characteristic differences. Preparation F45 yielded a peak value (1217 ng equivalents/ml) at 1.5 hr, and this value was much higher than those obtained for F160 and F500, which were 159 ng equivalents/ml at 4 hr and 83 ng equivalents/ml at 1 hr, respectively. From this result, it can be concluded that the relationship between the plasma level and particle size is particularly

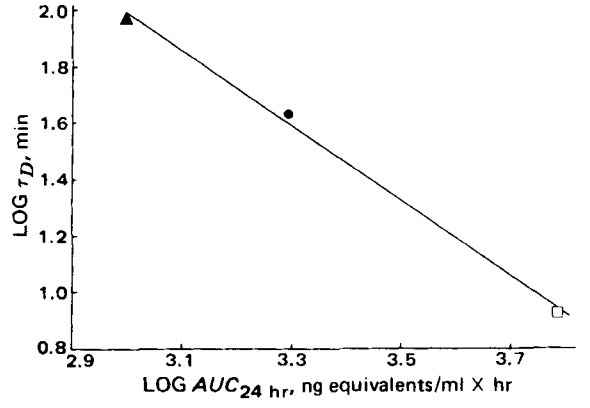

Figure 2—*Linear relationship between the logarithm of the area under the plasma level–time curve* (AUC) *and the logarithm of the mean value of the dissolution variable, τ_D, of proquazone for preparations F45 (45–74 μm, □), F160 (160–300 μm, ●), and F500 (500–1000 μm, ▲).*

critical when it exceeds a certain range, *i.e.*, 45–74 μm. The statistical analysis of the area under the curve (Table II) yielded the following sequence: $AUC_{F45} > AUC_{F160} > AUC_{F500}$. Figure 1 shows that for these preparations, there was a nearly linear relationship between the logarithm of the area under the curve and the logarithm of the mean particle size in the particle-size range investigated. Therefore, the dissolution of the drug in the intestines appears to constitute the rate-limiting step for the whole process of intestinal absorption; *i.e.*, $k_1 < k_2$.

Figure 2 shows a clear linear relationship between the logarithm of the area under the curve and log τ_D. The statistically significant difference between the area under the curve and τ_D for the preparations suggests that there is a genuine correlation between the *AUC* and the *in vitro* dissolution rate.

These results indicate that it may be possible, in principle, to estimate the *AUC* from the *in vitro* dissolution rate. The same correlation probably is obtained for any drug where dissolution is the rate-limiting step in absorption.

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COMMUNICATIONS

Correlation between Porosity and Dissolution Rate Constants for Disintegrating Tablets

Keyphrases □ Correlation coefficients—disintegrating tablets, relationship between porosity and dissolution rate □ Disintegration—tablets, correlation between porosity and dissolution rate □ Dissolution rate—correlation with porosity for disintegrating tablets □ Tablet disintegration—correlation between porosity and dissolution rate

To the Editor:

The importance of tablet porosity from a mechanical point of view has been discussed extensively (1, 2). Porosity also has been linked to the release characteristics of drugs from dosage forms and enters directly into the Higuchi square root law for dissolution (3). In the latter case, both penetration and diffusion characteristics are important.

There are cases in which tablets disintegrate and where the dissolution is relatively rapid so that the dissolution is a function of the disintegration (4, 5). However, there are cases in which tablets disintegrate fairly rapidly and where the dissolution is dictated by the rapid penetration of water into the granule. If the dissolution of the active ingredient and its diffusion out through the granule are rapid in relation to the penetration, then the dissolution is given by the amount of water that penetrates, *i.e.*, by an equation of the type described by Jost (6, 7):

$$\ln (m/m_0) = -k(t - t_i) \qquad \text{(Eq. 1)}$$

where m is the undissolved mass at time t, t_i is the disintegration time, and k is the dissolution constant (in reciprocal time units). Since the penetration rate is expected to be a function of the porosity, ϵ, of the tablet, then k also should be a function of ϵ. This argument assumes that the granules after disintegration have the same porosity as did the tablet before disintegration (8).

In a recent study in these laboratories, tablets were formed from granulations made by several processes: (*a*) fluid bed granulation[1], (*b*) chopper–ribbon blender[2], (*c*) chopper–ribbon blender followed by an oscillating granulator, and (*d*) chopper–ribbon blender followed by a rotating granulator[3]. The formula used was equal parts of dibasic calcium phosphate (anhydrous) and sulfanilamide granulated with 0.7 parts of 5% cornstarch paste. Drying was carried out to 1% loss on drying. Several differences were observed among these processes, and the phenomena related to dissolution and porosity will be discussed.

The granulations were screened and separated into four size fractions (<315, 315–400, 400–630, and >630 μm). Each fraction was compressed at three machine pressures (1200, 2400, and 3600 kg), and the resulting 12 batches of tablets from the four manufacturing procedures were subjected to dissolution tests by the beaker method (9). The porosities were measured using a mercury porosimeter.

The dissolution tests followed the relationship expressed in Eq. 1, and the prepared tablets had dissolution rate constants described by:

$$k = a_i + b_i\epsilon \qquad \text{(Eq. 2)}$$

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