similar to that after a 10-mg solution indicating that there were no dosage form or dose level effects on the extent of bioavailability of isosorbide dinitrate over the 5–20 mg dose range (*i.e.*, a similar relative fraction of the dose of isosorbide dinitrate reached the peripheral circulation unchanged after administration of each formulation). The mean adjusted AUC after administration of the sublingual 5-mg dose was significantly different from those after the oral tablet formulations, as might be expected. Indeed, previous studies have shown that the extent of bioavailability of isosorbide dinitrate from a sublingual formulation was at least twice that from the same formulation given orally (4), since some but not all of a sublingual dose avoids first-pass elimination. A large proportion of a sublingual dose is usually swallowed (18).

The conventional 95% confidence limits (21, 22) of mean areas expressed as a percent of the mean from the 10-mg solution formulation taken as a reference were −19 to +29%, −6 to +50%, and +32 to +109% from the 10-mg oral tablet, 20-mg oral tablet, and 5-mg sublingual tablet, respectively. These limits were −11 to +24% for the 5-mg oral tablet when the 10-mg oral tablet was taken as the reference (Table III). These confidence limits are fairly narrow even though plasma concentrations of isosorbide dinitrate can vary by several-fold between subjects, and the group of subjects studied was not particularly large.

Drug Half-Life—Isosorbide dinitrate kinetics appear to follow a "flip-flop" model (10, 18) and, therefore, the monoexponential decline of the concentrations in plasma can be regarded as reflecting the rate of drug absorption.

Among the orally administered formulations, the drug absorption half-life was shortest after the 10-mg solution dose, but only the drug half-life observed after the 20-mg tablet was significantly longer ($p < 0.01$) than that after the 10-mg solution. A shorter half-life after the sublingual dose would not be expected because the 5-mg tablet was retained in the mouth during disintegration before a notable proportion was swallowed. The half-lives measured in these studies are in close agreement with those reported in the literature (4, 9, 10, 18).

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Disintegrating Force as a New Formulation Parameter

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Abstract □ Some coated aspirin tablet formulations were evaluated by relating their properties to disintegrating force development patterns. The treatment of disintegrating force–time curves was effected using the Weibull distribution as proposed for dissolution. Such parameters as the maximum disintegrating force developed, the time needed to reach 63.2% maximum disintegrating force (τ_d) the shape parameter, the lag time, and the input value were used for evaluating the formulas examined. It was concluded that the input values, the integrating force development rate at time τ_d, can be employed as a new formulation parameter since, when correlated with the crushing strength, it allows an overall evaluation of the formula examined.

Keyphrases □ Disintegrating force—new formulation parameter, Weibull distribution, coated aspirin tablets □ Formulations—disintegrating force as a new parameter, Weibull distribution, coated aspirin tablets □ Weibull distribution—disintegrating force as a new formulation parameter, coated aspirin tablets

In a previous paper (1), the disintegrating force of tablets was defined as the force developed inside a tablet depending on the liquid–solid contact. It was shown that curves obtained by plotting disintegrating force *versus* liquid contact time had patterns following saturation kinetics dependent on the liquid penetration into voids. Since compact structure (defined by voids distribution and interparticle bonding) and disintegration–dissolution performance are strictly related, the investigations of the disintegration behavior of a tablet should provide a means for the evaluation of the structure obtained.

It is well known that disintegration time as measured by official apparatuses does not satisfactorily describe the disintegration properties of tablets, as demonstrated by the methods proposed to evaluate disintegration (2–5). Because disintegrating force–time curves could be related to the structure of tablets (6), these deserved a deeper investigation in view of their employment not only for studying the bioavailability-related properties of tablets, but also to assess the structure–technological parameter relationships.

The aim of the present work was to employ the disintegrating force parameters for studying coated aspirin tablet

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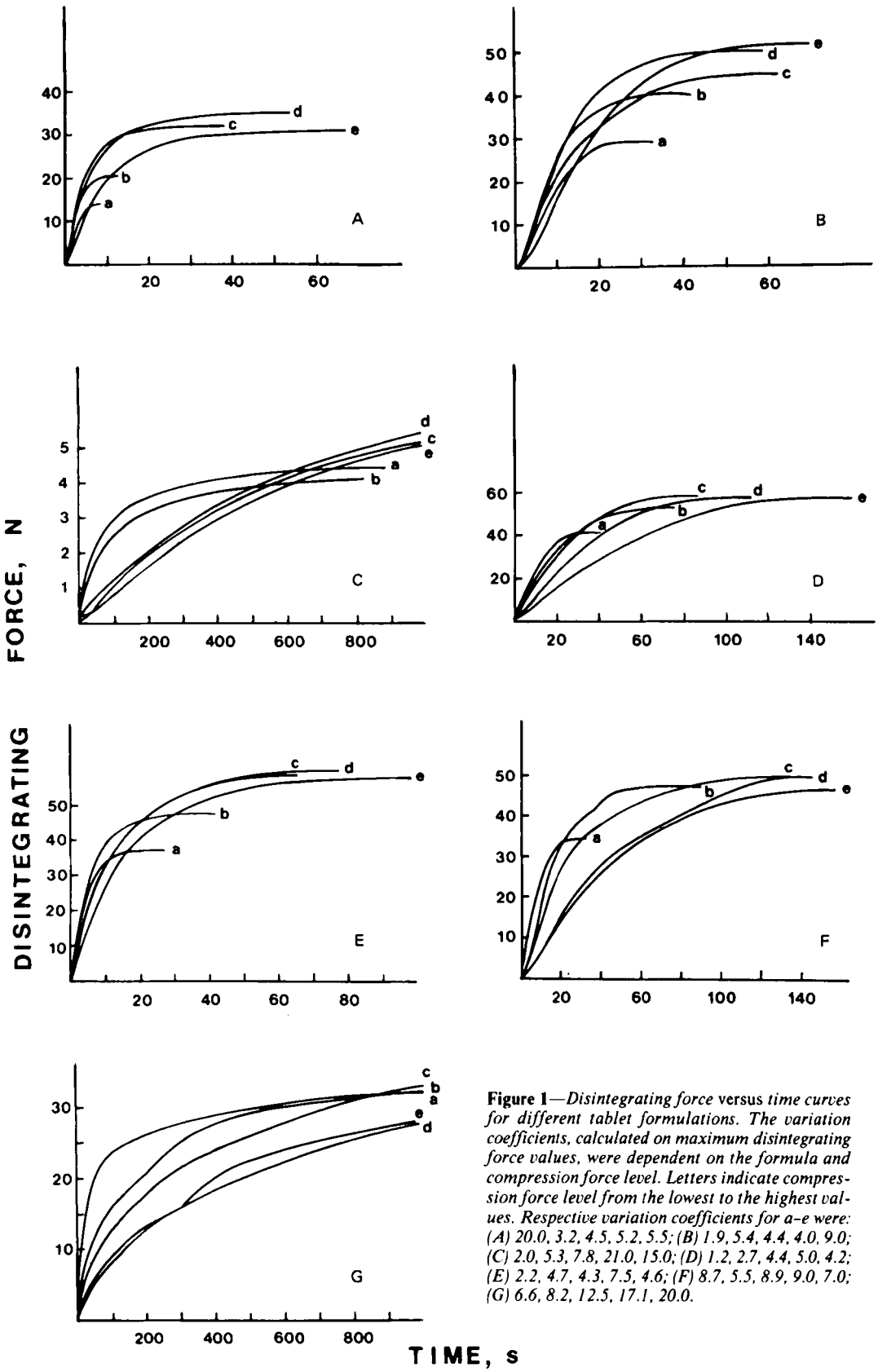

Figure 1—*Disintegrating force* versus *time curves for different tablet formulations. The variation coefficients, calculated on maximum disintegrating force values, were dependent on the formula and compression force level. Letters indicate compression force level from the lowest to the highest values. Respective variation coefficients for a–e were: (A) 20.0, 3.2, 4.5, 5.2, 5.5; (B) 1.9, 5.4, 4.4, 4.0, 9.0; (C) 2.0, 5.3, 7.8, 21.0, 15.0; (D) 1.2, 2.7, 4.4, 5.0, 4.2; (E) 2.2, 4.7, 4.3, 7.5, 4.6; (F) 8.7, 5.5, 8.9, 9.0, 7.0; (G) 6.6, 8.2, 12.5, 17.1, 20.0.*

formulations for the purpose of giving a new tool for a rational tablet formulation. The choice of coated aspirin as base material was justified by the results previously obtained when studying the influence of the disintegrating agent on the tablets' mechanical and release characteristics (7).

EXPERIMENTAL

Mixtures of coated aspirin as reported in Table I were prepared under controlled conditions with a compression apparatus[1]. The tablets were com-

[1] Turbula T2A.

Table I—Composition of the Coated Aspirin Mixtures (g/Tablet)

Mixture[a]	Coated Aspirin[b]	Cornstarch[c]	Mycrocrystalline Cellulose[d]	Crospovidone[e]	Modified Starch[f]	Cation-Exchange Resin[g]	Sodium Carboxymethylcellulose[h]
A	0.515	0.075	—	—	—	—	—
B	0.515	0.025	0.050	—	—	—	—
C	0.515	—	—		0.075	—	—
D	0.515	—	0.075	—	—	—	—
E	0.515	—	0.060	—	—	0.015	—
F	0.515	—	0.060	0.015	—	—	—
G	0.515	—	0.060	—	—	—	0.015

[a] All mixtures contained 2% (w/w) talc, F.U. grade. [b] Bayer Italy, Milan. [c] F.U. VIII Ed. grade. [d] Elcema G 250; Eigenmann-Veronelli, Milan. [e] Polyplasdone XL; GAF Italy, Milan. [f] STA-RX 1500; Eigenmann-Veronelli, Milan. [g] Amberlite IRP 88; C. Erba, Milan. [h] Nymcel ZSB 16; Nyma, Holland.

pressed at five different force levels and checked 24 h after compression for porosity, crushing strength, disintegration time (USP XX), and disintegrating force development using the apparatus previously described (1). The results are the mean of at least six determinations.

RESULTS AND DISCUSSION

The disintegrating force–time curves obtained for different formulations are given in Fig. 1. Some show a sigmoidal pattern (*e.g.*, mixture B), some are simple first-order exponential (*e.g.*, mixture E), and some present a steeper initial slope followed by a flattened "tail" in the final part (*e.g.*, mixture G). The analogy existing between these curves and dissolution curves from tablets suggested linearizing them in the way proposed (8) for dissolution, using the Weibull distribution rearranged into the form:

$$\log [-\ln (1 - F/F_\infty)] = b \log (t - t_0) - \log a \qquad \text{(Eq. 1)}$$

where F is the disintegrating force developed at time t and F_∞ is the maximum disintegrating force.

A plot of $[-\ln (1 - F/F_\infty)]$ *versus* t on log–log paper will give a straight line defined by the slope b, the ordinate intercept a, and the lag time t_0. The slope b characterizes the shape of the curve and is dependent on whether a sigmoidal, a simple first-order exponential, or an initially steeper exponential curve is considered. The parameter a can be replaced by the more informative disintegrating force time τ_d defined by:

$$a = (\tau_d)^b \qquad \text{(Eq. 2)}$$

where τ_d represents the time needed to obtain 63.2% of maximum disintegrating force, taken from the end of lag time t_0.

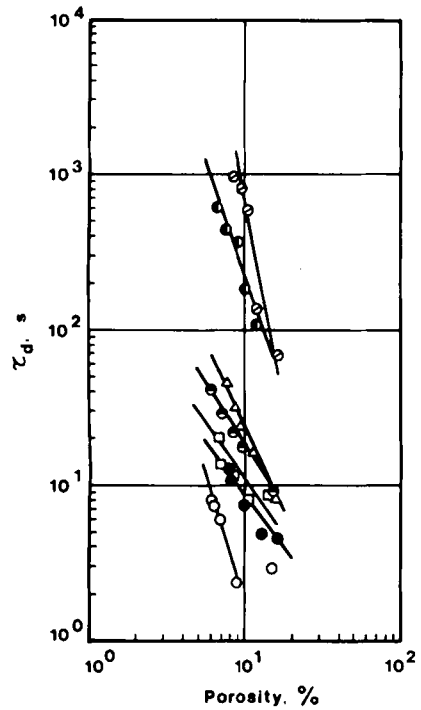

Figure 2—*Log–log plot of τ_d values* versus *porosity. Key: (○) A; (□) B; (⊘) C; (⊖) D; (●) E; (△) F; (◐) G.*

The evaluation of Weibull distribution parameters was performed by means of a program run on a computer[2]. Linear regression analysis, performed on the Weibull distribution rearranged into the form of Eq. 1, allowed the evaluation of b and a parameters. Experimental data were then fitted with a least-squares technique on the original $F(t)$ form of Weibull distribution. Numerical values of t_0, b, and a were estimated from the best fit of the experimental data. Uncertainty of a and b values was <1% ($p = 0.95$).

The results obtained for various mixtures examined are given in Table II. The maximum disintegrating force expresses the ability of the disintegrator, when contacting water, to push apart the bound particles. For the mixtures examined, the higher values of disintegrating force were obtained for E, F, and D, whereas smaller values were measured for C. The maximum disintegrating force increases as compression force increases, until an almost constant value is reached. This confirms that the swelling or repulsion energy of disintegrators can best work when particles are closer to one another (9). For mixture G, the disintegrating force-increasing pattern is not so evident. The disintegrating force development time (expressed by τ_d) always increases as compression force increases, and porosity decreases as shown in Fig. 2. Mixtures G and C have τ_d values markedly higher than the remaining mixtures at the same levels of compression force or porosity.

The comparison between maximum disintegrating force (F_∞) and disintegration time shows that a high value of maximum disintegrating force does not always correspond to a fast disintegration. For example, although mixtures G and A show comparable maximum disintegrating force values (at the highest compression force levels), their disintegration times are markedly different. In this case, τ_d seems to be the decisive factor. In other cases, the opposite situation is seen. The comparison between A (third compression force level) and G (fifth compression force level) mixtures shows that comparable

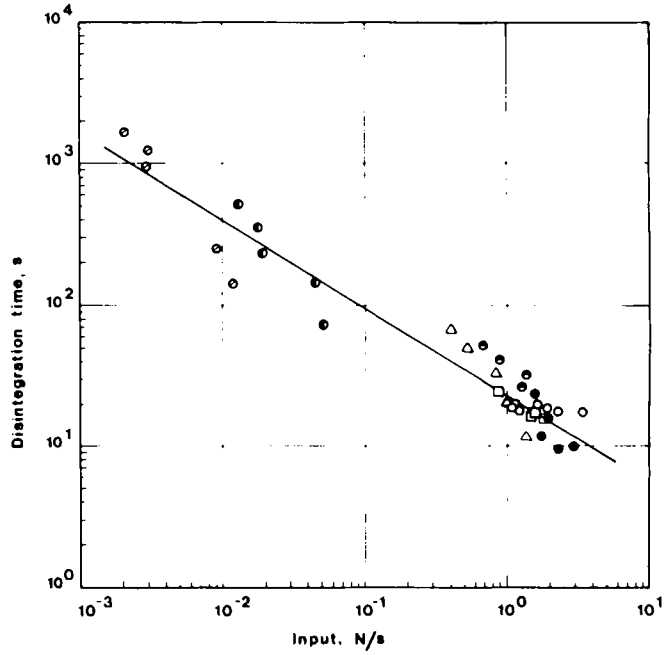

Figure 3—*Log–log plot of disintegration time* versus *input values. The linear regression equation is log* y = −0.6076·*log* x + 1.3925 (*r* = 0.968). *Key: (○) A; (□) B; (⊘) C; (⊖) D; (●) E; (△) F; (◐) G.*

[2] Minc-11 Digital.

Table II—Disintegration Time and Disintegrating Force Parameters of Different Tablets

Mixture	Compression Force, hN	Disintegration Time, s	Disintegrating Force (F_∞), N	τ_d, s	Shape Parameter (b)
A	43	18	14	3	1.3
	79	18	18	2	1.0
	154	19	31	6	1.0
	186	18	34	7	0.7
	280	19	34	8	0.7
B	56	18	26	8	1.3
	93	16	33	8	1.2
	145	17	40	11	1.1
	196	20	42	14	1.0
	251	25	43	20	1.1
C	53	146	4	70	0.6
	72	256	5	140	0.7
	135	964	5	610	1.0
	164	1223	6	840	1.3
	287	1695	5	990	1.2
D	50	20	37	9	1.1
	102	27	51	18	1.2
	135	32	56	21	1.4
	193	41	58	29	1.2
	274	53	52	42	1.5
E	66	9	34	5	0.9
	89	10	42	5	0.9
	130	12	47	8	0.8
	170	16	53	11	1.1
	242	24	50	13	1.1
F	44	12	34	9	1.0
	92	21	44	16	1.0
	144	34	53	24	1.0
	188	49	50	33	0.9
	252	66	48	48	1.1
G	62	72	28	110	0.5
	104	143	32	185	0.7
	127	237	32	380	0.6
	177	359	32	450	0.7
	223	505	27	630	0.8

τ_d values correspond to disintegration time values 50% of the other due to differences in disintegrating force values. The above examples clearly indicate that disintegration time depends on both parameters. As previously indicated (6), the joint consideration of F_∞ and τ_d allows an evaluation of the kinetic aspect of the disintegrating force development, which, as recently outlined (10), seems to be the factor governing the disintegration process. The derivative of the Weibull equation at time $t = t_0 + \tau_d$, termed "input," was calculated and employed for the quantitative evaluation of disintegration kinetics.

The good correlation found between input and disintegration time, as expressed in Fig. 3, indicates that it is the disintegrating force development rate that determines the disintegration of the compact. Input depends on compression force (Fig. 4), and a complete characterization of the compact can

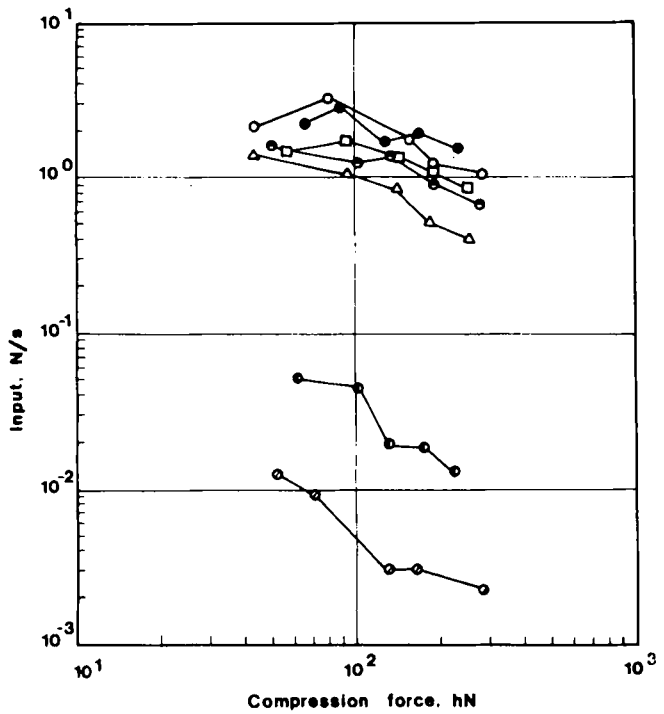

Figure 4—*Log-log plot of input values* versus *compression force. Key: (○) A; (□) B; (⊘) C; (⊖) D; (●) E; (△) F; (◐) G.*

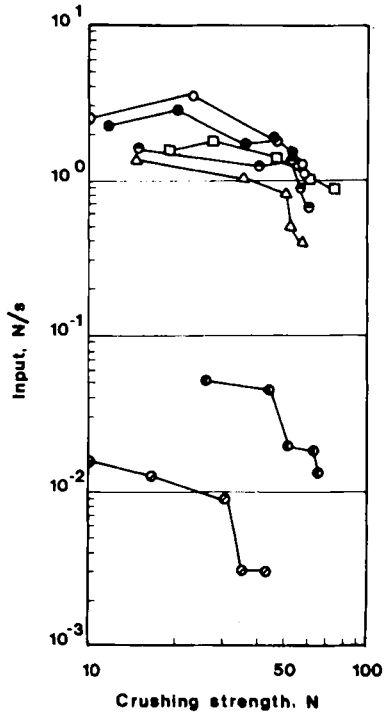

Figure 5—*Log-log plot of input* versus *crushing strength. Key: (○) A; (□) B; (⊘) C; (⊖) D; (●) E; (△) F; (◐) G.*

be obtained by plotting crushing strength *versus* input values (Fig. 5). The graphs allow a visual determination of mixtures for which the crushing strength can be increased without significantly reducing the input value. Mixtures A, E, and B, for which an increase in crushing strength does not correspond to a marked decrease in input values, are easy to handle. For mixtures C and G, the increase of crushing strength corresponds to a concomitant marked reduction of input values, as evidenced by curve slopes. Mixtures F and D show a limiting value of crushing strength above which a little increase causes a large decrease of the input value.

The shape parameter b (Eq. 1) seems to be linked to the disintegration process in the following way:

1. An S-shaped disintegrating force development curve ($b > 1$) indicates the presence of an initial obstacle to water penetration linked to the surface conditions of the tablet.
2. A steeper initial slope in the disintegrating force development curve ($b < 1$) can indicate the presence of an obstacle to water penetration arising inside the tablet.
3. An exponential disintegrating force development curve ($b = 1$) indicates a regular fluid penetration.

The situation relative to $b < 1$ is more critical, since resistence to fluid penetration arising inside the tablet may lead to considerable delay in disintegration, whereas for $b > 1$, the small values of time lag found in the cases examined indicate that the tablet surface conditions do not influence disintegration time too much.

For the mixtures examined, b values depend on compression force and reflect the changes in compact structure. Mixture G shows b values constantly <1, thus enabling the presumption that disintegrator gelatinization enhances the resistance to fluid penetration. Mixtures D, F, B, and E show b values of ~ 1, thus indicating a regular disintegrating force development. Mixtures A and C show the opposite behavior. For the former, b values decrease as compression force increases. This is consistent with the product compression behavior, *i.e.*, starch granules deformed by compression readily absorb water forming a viscosity-increasing gel[3]. For the latter, the poor absorption is likely to be influenced by porosity conditions, thus enhancing the initial hindrance to water penetration. The results obtained indicate that, of the various mixtures examined, A, B, and E show the best overall performances.

CONCLUSIONS

The measurement of disintegrating force provides a deeper insight into the tablet structure obtained by processing a given formula. Whereas a "static" structure evaluation can be obtained through porosity, pore size distribution, *etc.*, disintegrating force measurements allow a "dynamic" evaluation of the structure itself, linked to the disintegration process and consequent active ingredient liberation. The input value, *i.e.*, the disintegrating force development rate at time $t = t_0 + \tau_d$, can be employed as a new parameter for tablet formulation. It is very sensitive to formulation and tablet structure changes and, if correlated with the crushing strength, allows an overall evaluation of the formula examined. The measure of the shape parameter b is a good reflection of the conditions of the compact and completes the structural information on tablet structure. On the basis of the results obtained, it seems justified to propose the measure of the disintegrating force as a very useful and decisive means for formulation evaluation.

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Disposition of Ibuprofen in Nephrectomized Dogs

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Received August 26, 1982, from the **Department of Pharmaceutics, College of Pharmacy, University of Houston*, and ‡*Infectious Disease and Clinical Microbiology Program, University of Texas Medical School, Houston, TX 77030.* Accepted for publication March 17, 1983.

Abstract □ The pharmacokinetics of ibuprofen were studied in four nephrectomized and three normal dogs after administration of 214.3–227.6 mg iv of ibuprofen. Blood samples were collected at various time intervals for up to 10 h and serum concentrations of ibuprofen were assayed by an HPLC method. The elimination of serum ibuprofen followed first-order kinetics, with mean half-lives of 2.51 ± 1.10 and 2.81 ± 0.72 h in normal and nephrectomized dogs, respectively. Mean serum clearance of ibuprofen in nephrectomized dogs, 31.0 ± 5.2 mL/h/kg, was higher than that in normal dogs, 12.2 ± 8.6 mL/h/kg, ($p < 0.02$). The difference may be attributed to the greater volume of distribution for ibuprofen in nephrectomized dogs, 125.2 ± 39.0 (88.8–160.4) mL/kg as compared with 53.4 ± 57.8 (26.0–119.9) mL/kg in the normal group ($p < 0.2$).

Keyphrases □ Ibuprofen—disposition in nephrectomized dogs, pharmacokinetics □ Disposition—ibuprofen, nephrectomized dogs, pharmacokinetics □ Pharmacokinetics—disposition of ibuprofen in nephrectomized dogs

Ibuprofen, (±)-2-(*p*-isobutylphenyl)propionic acid (I), is a nonsteroidal anti-inflammatory agent indicated primarily for rheumatic diseases (1). The pharmacokinetics of I have been studied in normal volunteers. The drug is readily absorbed orally, and plasma peak levels are reached within 2 h of administration. The elimination of I from plasma is first order with apparent half-lives of 1.4–2.5 h (2–6). Similar half-lives are observed in arthritic patients, suggestive of no tissue accumulation of I in rheumatic patients (2). Patients with chronic circulatory insufficiency exhibit pharmacokinetic parameter values comparable with those of healthy subjects (7).

The metabolism of I has been studied in humans and several