Table V—Rate of Intake of Mercury Compounds from Cysteine [a]

Mercury Compounds	Time, min	Reaction, %
Mercuric chloride	10	95
Mercuric chloride	60	97
Mercuric chloride	240	99
Mercuric chloride	1320	100
Methyl mercury chloride	10	91
Methyl mercury chloride	60	91
Methyl mercury chloride	240	91

[a] Mercury compounds (20 ppm Hg) were stirred for 2 hr with 20 ml of 10^{-2} *M* cysteine in phosphate-buffered saline solution. Chelating microspheres were then added (20 mg in the reaction with methyl mercury chloride and 50 mg in the reaction with mercuric chloride). In control experiments the loss of mercury compounds was negligible.

as an oral antidote for treatment in cases of heavy metal poisoning, due to their high surface area. As a model, the potential of polymercaptal microspheres for mercury poisoning was demonstrated *in vitro* and future experiments will have to be carried out *in vivo* as well. Moreover, the affinity of chelating microspheres toward other heavy metallic compounds such as arsenic, cadmium, lead, and copper, *etc.*, will be investigated to evaluate their potential use for treatment of poisoning with these heavy metals.

REFERENCES

(1) T. Aaronson, *Environment*, **13**, 16 (1971).

(2) N. Nelson *et al.*, *Environ. Res.*, **4**, 1 (1971).

(3) N. Grant, *Environment*, **13**, 2 (1971).

(4) W. G. Levine, in "The Pharmacological Basis of Therapeutics," L. S. Goodman and A. Gilman, Eds., Macmillan, New York, N.Y., 1975, pp. 912, 923.

(5) E. Friedheim and C. Corvi, *J. Pharm. Pharmacol.*, **27**, 624 (1975).

(6) M. M. Jones, L. T. Burka, M. E. Hunter, M. Basinger, G. Campo, and A. D. Weaver, *J. Inorg. Nucl. Chem.*, **42**, 775 (1979).

(7) T. W. Clarkson, *Arch. Environ. Health*, **26**, 173 (1973).

(8) H. Takahashi and K. Hirayama, *Nature (London)*, **232**, 201 (1971).

(9) J. J. Benes, J. Stanberg, J. Peska, M. Tichy, and M. Cikrt, *Die Angewandte Makromolekular Chemie*, **44**, 67 (1975).

(10) A. Campe, N. Veighe, and A. Claeys, *At. Absorp. Newsl.*, **17**, 100 (1978).

(11) S. L. Law, *Science*, **174**, 285 (1971).

(12) G. A. Nyssen, M. M. Jones, J. D. Hernigan, D. R. Harbison, and J. S. MacDonald, *J. Inorg. Nucl. Chem.*, **39**, 1889 (1977).

(13) F. Bakir, *et al.*, *Science*, **181**, 230 (1973).

(14) S. Margel, S. Zisblat, and A. Rembaum, *J. Immunol. Methods*, **28**, 341 (1979).

(15) A. Rembaum and S. Margel, *Br. Polym. J.*, **10**, 275 (1978).

(16) K. J. Widder, A. E. Senyei, and D. G. Scarpelli, *Proc. Soc. Exp. Biol. Med.*, **158**, 141 (1978).

(17) J. M. Singer, *Am. J. Med.*, **31**, 766 (1961).

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Relative Bioavailability of Commercially Available Ibuprofen Oral Dosage Forms in Humans

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Abstract □ Two human bioavailability studies were conducted to assess the *in vivo* performances of recently marketed 200-, 300-, and 400-mg ibuprofen capsules relative to the innovator's 300- and 400-mg tablets when administered as single oral 300- or 400-mg doses. An ibuprofen oral solution was also administered in each trial. Within each study, the products were equivalent to each other and to the oral solution with respect to the extent of ibuprofen absorption. Absorption rates, however, differed markedly among the products studied. Ibuprofen was more slowly absorbed from the 300- and 400-mg capsules than from the respective strength tablets. The 200-mg capsule exhibited an absorption rate comparable to the 400-mg tablet but more rapid than the 400-mg capsule. It was concluded that two of the duplicator's 200-mg capsules were bioequivalent to one of the innovator's 400-mg tablet. The duplicator's 300- and 400-mg capsules were bioinequivalent to the innovator's 300- and 400-mg tablets, respectively, due to their slower rates of absorption.

Keyphrases □ Bioavailability—commercially available ibuprofen oral dosage forms in humans □ Ibuprofen—bioavailability of commercially available oral dosage forms in humans □ Dosage forms, oral—bioavailability of commercially available ibuprofen in humans

Ibuprofen is a propionic acid derivative with anti-inflammatory, analgesic, and antipyretic activities and is widely utilized in the treatment of osteoarthritis, rheumatoid arthritis, and mild to moderate pain (1, 2). Recently, it has become a multiple-source drug product in Canada; thus, the question arises whether the new products are equivalent relative to the quality and performance of the innovator's products. Of particular importance is their *in vivo* performance in terms of the extent and rate of ibuprofen GI absorption from the solid oral dosage forms.

A previous study demonstrated the bioequivalence of a pilot plant lot of the 300-mg capsule product to the innovator's 300-mg tablet (3). The present studies were conducted to assess the bioavailability of full-scale production lots of the recently introduced 200-, 300-, and 400-mg capsules relative to the innovator's 300- and 400-mg tablets.

EXPERIMENTAL

Products Studied—Two comparative bioavailability studies were conducted to evaluate the five commercially available ibuprofen products (A, B, C, D, and E) listed in Table I.

An aqueous solution of sodium ibuprofen (F, Table I) was utilized as a reference standard to which the other formulations could be compared. With the exception of the solution, the products were obtained from usual commercial sources without any attempt to procure or select specific lots.

The ibuprofen dosage forms were administered as single, oral 300-mg doses in Study I and as single, oral 400-mg doses in Study II.

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Table I—Description of Ibuprofen Dosage Forms Tested

Formulation Type	Lot Number	Formulation Code
Capsule, 300 mg[a]	8E08N	A
Tablet, 300 mg[b]	E284	B
Capsule, 400 mg[a]	9D079	C
Capsule, 200 mg[a]	8E07N	D
Tablet, 400 mg[b]	E426	E
Solution, 20 mg/ml[c]	18,025-6	F

[a] Amersol capsules; manufactured and marketed by Frank W. Horner Ltd., Montreal, Quebec, Canada. [b] Motrin tablets; manufactured and marketed by The Upjohn Co. of Canada, Don Mills, Ontario, Canada. [c] Manufactured by The Upjohn Co., Kalamazoo, Mich.

Human Subjects—Eighteen normal volunteers between the ages of 18 and 35 years and 20 normal volunteers between the ages of 20 and 33 years were selected to participate in Study I and Study II, respectively. They were accepted into the studies following informed consent, a physical examination, and blood and urine analyses.

Study Design—In Study I, Formulations A, B, and F were administered according to a 3 × 3 Latin-square crossover design with six replications. In Study II, Formulations C, D, E, and F were administered according to a 4 × 4 Latin-square crossover design with five replications (Table II). The ibuprofen doses were separated by 4 days. Each dose was administered with 180 ml of water following an overnight fast. The fasting period continued for 2 hr following the dose. No food or beverage other than water was permitted during the fasting period.

Blood (7 ml) was collected from a forearm vein by individual venipunctures just prior to dosing and at 0.17 (10 min), 0.33 (20 min), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hr following drug administration. Serum was harvested from the blood samples ~40 min after collection, immediately frozen, and kept in a frozen state until assayed.

The serum specimens were quantitatively analyzed for unchanged ibuprofen utilizing GLC with flame ionization detection as described previously (4).

THEORETICAL

Symbols—The following symbols were used in the calculations and are defined as follows:

- AUC_t = area under the serum ibuprofen concentration–time curve from time zero through time t
- AUC_∞ = area under the serum ibuprofen concentration–time curve from time zero through infinite time
- $AUMC_t$ = area under the (first) moment curve from time zero through time t
- $AUMC_\infty$ = area under the (first) moment curve from time zero through infinite time
- C_t = ibuprofen serum concentration at time t (measured)
- $\hat{C}_t$ = ibuprofen serum concentration at time t (calculated)
- C_{max} = peak ibuprofen serum concentration
- CFA_{rel} = cumulative fraction absorbed relative to the oral solution
- MDT = mean *in vivo* dissolution time
- MRT = mean residence time
- t = elapsed time after ibuprofen administration
- T = time at which the last measurable ibuprofen serum concentration (≥1.0 μg/ml) was observed
- t_{max} = time at which C_{max} occurred
- λ_z = apparent ibuprofen elimination rate constant

Model Independent Parameters—AUC_t and $AUMC_t$ were calculated by trapezoidal rule. Extrapolations through infinite time utilized:

$$AUC_\infty = AUC_T + \frac{\hat{C}_T}{\lambda_z} \quad \text{(Eq. 1)}$$

$$AUMC_\infty = AUMC_T + \left[T + \frac{1}{\lambda_z}\right]\frac{\hat{C}_T}{\lambda_z} \quad \text{(Eq. 2)}$$

The apparent elimination rate constant (λ_z) was estimated by fitting the ibuprofen serum concentrations following administration of the oral solution (Formulation F) to a biexponential equation using nonlinear least-squares regression (NONLIN) (5). Estimates of $\hat{C}_T$ following administration of Formulation F were calculated from the same biexponential equation. Estimates of $\hat{C}_T$ following administration of the solid dosage forms were calculated from the equation of the line resulting from linear least-squares regression of $\ln C_t$ *versus* t using those data points in the terminal log-linear region. Attempts to estimate λ_z from the slope of that line resulted in significantly smaller values for Capsules A and C (Table III), suggesting prolonged GI absorption of ibuprofen. The elimination rate constant estimated from the oral solution data was considered a more reliable description of the elimination rate and was utilized in all subsequent calculations. This decision required the assumptions that λ_z remained constant for each volunteer throughout the study and that absorption was essentially complete by 12 hr following drug administration.

Table II—Latin-Square Crossover Designs for Ibuprofen Bioavailability Studies

Study I (Dose = 300 mg)

Group	Subjects	Formulation Phase I	Phase II	Phase III
1	5, 7, 8, 10, 13, 16	A	B	F
2	1, 2, 4, 6, 12, 18	B	F	A
3	3, 9, 11, 14, 15, 17	F	A	B

Study II (Dose = 400 mg)

Group	Subjects	Formulation Phase I	Phase II	Phase III	Phase IV
1	2, 10, 17[a], 18, 20	C	D	F	E
2	7, 13, 14, 15, 19	D	E	C	F
3	1, 4, 9, 11, 16	E	F	D	C
4	3, 5, 6, 8, 12	F	C	E	D

[a] Subject dropped from study following Phase I for reasons unrelated to the study.

The mean residence time of drug in the body (MRT) was calculated using (6):

$$MRT = \frac{AUMC_\infty}{AUC_\infty} \quad \text{(Eq. 3)}$$

The difference between the MRT for a solid oral dosage form and the

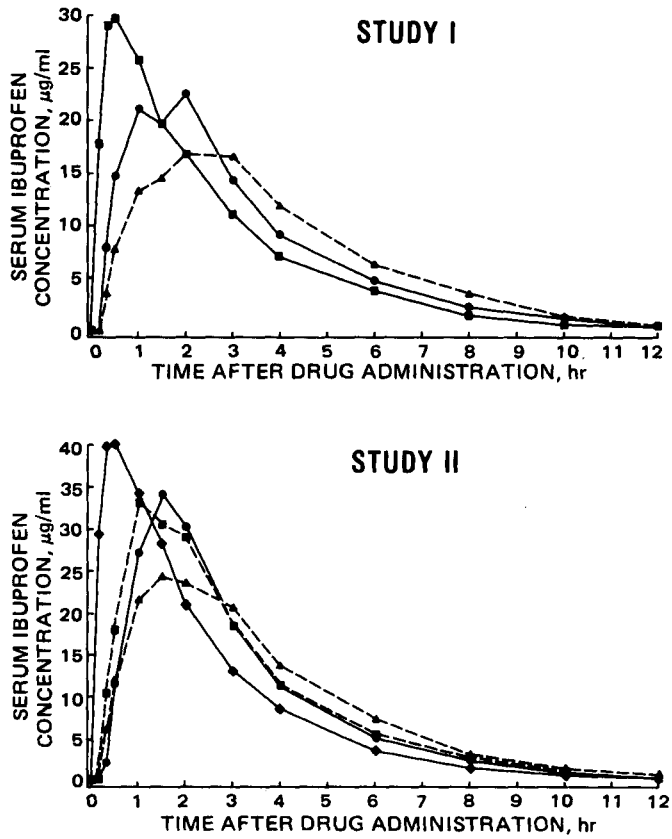

Figure 1—*Mean serum ibuprofen concentration–time curves. Key: Study I: (▲) 300-mg capsule (A); (●) 300-mg tablet (B); (■) oral solution (F); Study II: (▲) 400-mg capsule (C); (■) 200-mg capsule (D); (●) 400-mg tablet (E); (◆) oral solution (F).*

Table III—Mean Serum Ibuprofen Concentrations and Related Parameters

Study I ($N = 18$)

	Formulation			p^a	Pairwise[b] Comparisons
	A	B	F		
C_t, μg/ml at:					
0.0 hr	0.00	0.00	0.00	—	
0.167	0.06	0.16	17.8	< 0.0001	F B A
0.333	3.59	7.96	29.0	< 0.0001	F B A
0.5	7.79	14.7	29.7	< 0.0001	F B A
1	13.3	21.1	25.7	0.0066	F B A
1.5	14.5	19.6	19.7	0.075	F B A
2	16.9	22.5	17.0	0.0021	B F A
3	16.6	14.3	11.0	< 0.0001	A B F
4	11.9	9.09	7.10	< 0.0001	A B F
6	6.31	4.76	3.82	0.0006	A B F
8	3.54	2.25	1.44	< 0.0001	A B F
10	1.36	1.23	0.57	0.018	A B F
12	0.63	0.46	0.38	0.23	A B F
AUC_∞, μg hr/ml	91.5	89.9	88.5	0.75	A B F
C_{max}, μg/ml	21.1	32.4	31.9	< 0.0001	B F A
t_{max}, hr	2.17	1.32	0.46	< 0.0001	A B F
λ_z, hr^{-1}	0.347	0.414	0.455	0.0002	F B A

Study II ($N = 18$)

	Formulation				p^a	Pairwise[b] Comparisons
	C	D	E	F		
C_t, μg/ml at:						
0.0 hr	0.00	0.00	0.00	0.00	—	
0.167	0.12	0.22	0.06	29.4	< 0.0001	F D C E
0.333	6.09	10.4	2.12	39.7	< 0.0001	F D C E
0.5	12.0	18.0	11.4	40.0	< 0.0001	F D C E
1	21.6	33.1	27.1	34.2	0.0067	F D E C
1.5	24.3	30.5	34.1	28.2	0.0058	E D F C
2	23.5	29.0	30.2	21.0	0.0001	E D C F
3	20.7	18.4	18.7	13.0	0.0030	C E D F
4	13.7	11.4	11.1	8.51	0.0006	C D E F
6	7.33	5.58	5.06	3.58	< 0.0001	C D E F
8	3.11	2.61	2.42	1.55	0.0022	C D E F
10	1.52	1.10	0.92	0.72	0.025	C D E F
12	0.91	0.36	0.48	0.29	0.0074	C E D F
AUC_∞, μg hr/ml	116	119	112	110	0.48	D C E F
C_{max}, μg/ml	31.4	39.0	37.9	45.5	< 0.0001	F D E C
t_{max}, hr	2.00	1.25	1.39	0.53	< 0.0001	C E D F
λ_z, hr^{-1}	0.364	0.390	0.415	0.499	< 0.0001	F E D C

[a] Level of significance for test of equal treatment means. [b] The means for formulations connected by overhead bars were not significantly different ($p > 0.05$).

MRT for an oral solution (Eq. 4) has been termed the mean *in vivo* dissolution time (MDT) by Riegelman and Collier (7):

$$MDT = MRT_{solid} - MRT_{solution} \quad \text{(Eq. 4)}$$

Theoretically, MDT is an estimate of the mean time which a drug molecule remains as a solid in the GI tract. In reality, MDT is probably not an absolute estimator of dissolution rate due to the differing influences of stomach emptying rate on solid and solution dosage forms. It is, nonetheless, an excellent tool for comparing absorption rates among treatments administered to the same subjects in a bioavailability trial.

Model Dependent Parameters—The serum ibuprofen concentrations following the administration of the oral solution to each subject were well described by a biexponential equation. This indicated that the pharmacokinetics of ibuprofen could be explained in terms of a one-compartment open model. As a result, cumulative absorption profiles could be constructed according to the method of Wagner and Nelson (8). *Modification* of that method resulted in Eq. 5, which was utilized to estimate the cumulative amount of ibuprofen absorbed from the solid dosage form divided by the total amount absorbed from the oral solution, *e.g.*, cumulative fraction absorbed relative to the oral solution (CFA_{rel}):

$$CFA_{rel} = \frac{C_t + \lambda_z [AUC_t]}{\lambda_z [AUC_{\infty}^{solution}]} \quad \text{(Eq. 5)}$$

Estimates of cumulative fraction absorbed relative to the oral solution (CFA_{rel}) provided both visual and statistical comparisons of absorption rate and extent among the treatments.

Statistical Comparisons—Within each study, statistical comparisons of C_t, C_{max}, t_{max}, and AUC_∞ data were performed utilizing ANOVA with group, subject within group, phase, and treatment as factors. In cases where treatment effects were significant ($p < 0.05$), pairwise comparisons were evaluated with Tukey's multiple range test. A two-tailed paired t test was applied to MDT and CFA_{rel} data from Study I. The described ANOVA model was utilized to evaluate MDT and CFA_{rel} data from Study II except that the pairwise comparisons were performed using linear contrasts of the regression coefficients resulting from the ANOVA (9).

Table IV—Mean Estimates of Cumulative Fraction Absorbed Relative to the Oral Solution (CFA_{rel}) and Mean *In Vivo* Dissolution Time (*MDT*)

Study I (N = 18)

	Formulation A	Formulation B	p^a
CFA_{rel} at:			
0.0 hr	0.00	0.00	—
0.167	0.00	0.00	0.16
0.333	0.10	0.23	0.16
0.5	0.22	0.44	0.071
1	0.43	0.73	0.046
1.5	0.55	0.79	0.044
2	0.70	0.96	0.0023
3	0.89	0.96	0.15
4	0.93	0.96	0.54
6	1.00	1.00	0.89
MDT, hr	1.44	0.73	0.0052

Study II (N= 18)

	Formulation C	Formulation D	Formulation E	p^a	Pairwise[b] Comparisons
CFA_{rel} at:					
0.00 hr	0.00	0.00	0.00	—	
0.167	0.00	0.00	0.00	0.51	C D E
0.333	0.13	0.21	0.04	0.028	D C E
0.5	0.25	0.38	0.23	0.16	D C E
1	0.52	0.77	0.63	0.021	D E C
1.5	0.68	0.88	0.91	0.012	E D C
2	0.78	0.99	0.99	0.0056	D E C
3	0.93	1.02	1.00	0.0052	D E C
4	0.97	1.03	0.99	0.12	D E C
6	1.04	1.08	1.02	0.25	D C E
MDT, hr	1.27	0.80	0.79	0.0016	C D E

[a] Level of significance for test of equal treatment means. [b] The means for formulations connected by overhead bars were not significantly different ($p > 0.05$).

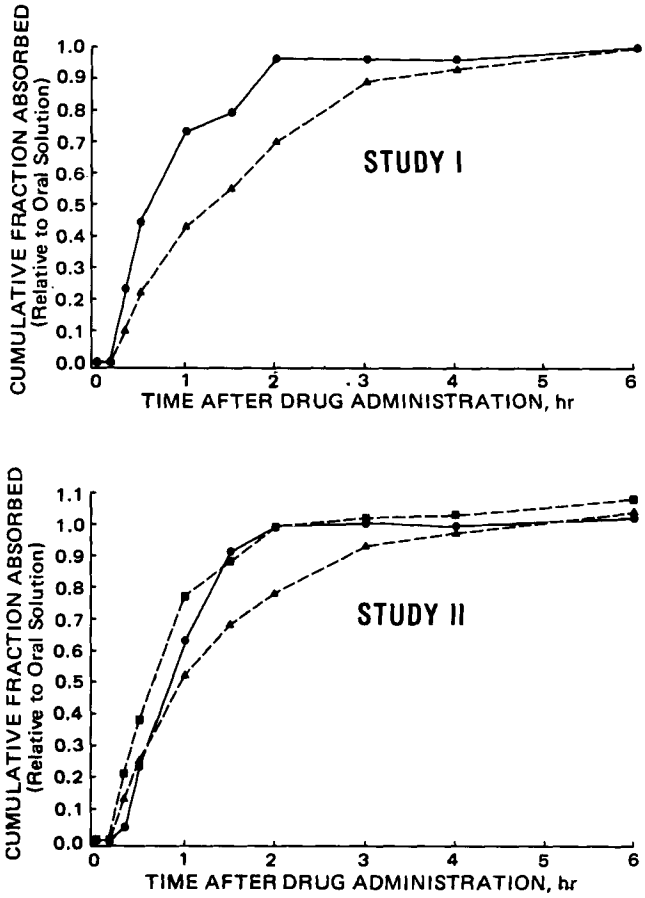

Figure 2—*Modified Wagner-Nelson absorption plots of mean cumulative fraction absorbed relative to the oral solution* (CFA_{rel}) versus *time. Key: Study I: (▲) 300-mg capsule (A); (●) 300-mg tablet (B); Study II: (▲) 400-mg capsule (C); (■) 200-mg capsule (D); (●) 400-mg tablet (E).*

RESULTS

All 18 subjects enrolled in Study I successfully completed the three treatment phases. Of the 20 subjects enrolled in Study II, one (Subject 17) discontinued participation following Phase I for reasons unrelated to the study. Another (Subject 18) exhibited such unusual ibuprofen concentration–time courses that the person was considered unrepresentative of a normal subject population. Neither of these subjects' results were utilized in any subsequent data analyses.

Concentration at Each Sampling Time (C_t)—Table III and Fig. 1 present the mean serum ibuprofen concentrations at each sampling time which resulted from the administration of Formulations A, B, and F as single, oral 300-mg doses in Study I and formulations C, D, E, and F as single, oral 400-mg doses in Study II.

In Study I, statistically significant ($p < 0.05$) differences were observed among the treatments at all but two sampling times. The pairwise comparisons indicated that those differences were predominantly the result of a concentration–time profile for the oral solution which differed markedly from those for the two solid dosage forms. Tablet B, however, did exhibit significantly lower concentrations than Capsule A at 2, 4, 6, and 8 hr following drug administration.

In Study II, statistically significant differences among the formulations were observed at each sampling time. Most of those differences were attributable to solid dosage form *versus* solution comparisons. Concentrations following Capsule C administration did differ significantly from those following Capsule D administration at 1, 6, and 12 hr, and from those following Tablet E administration at 1.5, 2, and 6 hr postdose. No significant differences were observed for Formulations D *versus* E comparisons at any sampling time.

Area Under the Concentration–Time Curve (AUC_∞)—The average areas under the serum ibuprofen concentration–time curves (AUC_∞) resulting from administration of each formulation are also shown in Table III. Within each study, no statistically significant differences were observed among the formulations. The following ratios of mean AUC_∞ for the solid dosage forms to the mean AUC_∞ for the oral solution were observed:

A/F	B/F	C/F	D/F	E/F
1.03	1.02	1.05	1.08	1.01

Those results indicated that the tablet and capsule products were equivalent to each other and to the oral solution with respect to the extent of ibuprofen absorption.

Peak Concentration (C_{max}) and Peak Time (t_{max})—Statistical analyses of the C_{max} and t_{max} values observed following the administration of the various ibuprofen formulations (Table III) yielded significant differences among the treatment means in both studies. The oral solution exhibited the most rapid rate of absorption with an average t_{max} in both studies of ~0.5 hr and average C_{max} estimates of 31.9 and 45.5 μg/ml in Studies I and II, respectively.

In Study I, the 300-mg capsule (A) resulted in an average C_{max} which was 35% less and a t_{max} which was 64% greater than those achieved by the 300-mg tablet (B). Those differences were statistically significant and indicated that ibuprofen was more rapidly absorbed from the tablet than from the capsule.

In Study II, the results of pairwise comparisons between the 400-mg tablet (E) and capsule (C) were similar to those seen in Study I for the 300-mg formulations. Capsule C produced an average C_{max} which was 17% less and a t_{max} which was 44% greater than those resulting from Tablet E. Only the t_{max} difference was statistically significant. The mean C_{max} and t_{max} results for the 200-mg capsule (D) were similar to those for the 400-mg tablet (E) and significantly different from those for the 400-mg capsule (C). These results indicated that Formulations D and E were absorbed at similar rates and that both were absorbed more rapidly than Formulation C.

Mean *In Vivo* Dissolution Time (*MDT*)—The average *MDT* estimates shown in Table IV distinguish the solid dosage forms on the basis of absorption rate. The 300-mg capsule (A) exhibited an average *MDT* nearly twice that for the 300-mg tablet (B) (1.44 *versus* 0.73 hr). In Study

II, the 200-mg capsule (D) and the 400-mg tablet (E) resulted in approximately equal *MDT* estimates (0.80 *versus* 0.79 hr). The 400-mg capsule (C), however, was more slowly absorbed with an average *MDT* of 1.27 hr. The differences for the pairwise comparisons of A *versus* B, C *versus* D, and C *versus* E were statistically significant.

Cumulative Fraction Absorbed Relative to the Oral Solution (CFA_{rel})—Modified Wagner-Nelson plots of mean CFA_{rel} *versus* time for the ibuprofen products are presented as Fig. 2. Inspection of the plots suggests that, on the average, Formulations A and C required 4–6 hr to achieve an extent of absorption within 95% of the oral solution. Formulations B, D, and E, however, reached the same endpoint by the 2-hr sampling time.

Statistical comparisons of the CFA_{rel} estimates at each sampling time up to 6 hr are shown in Table IV. The 300-mg tablet (B) resulted in significantly greater mean CFA_{rel} values at 1, 1.5, and 2 hr than the 300-mg capsule (A). The 400-mg tablet (E) and the 200-mg capsule (D) exhibited similar mean CFA_{rel} estimates with a significant difference occurring only at the 20-min sampling time. The 400-mg capsule (C) results were significantly less than those for Formulation D at 1, 1.5, 2, and 3 hr and those for Formulation E at 1.5, 2, and 3 hr. Since no differences were observed in the extent of absorption among the products studied, the relatively low estimates of CFA_{rel} resulting from Formulations A and C were indicative of their slower rates of absorption.

DISCUSSION

Though all of the commercially available ibuprofen products studied were equivalent with respect to the amount of drug absorbed from the dosage forms, they differed markedly in terms of absorption rate. Specifically, the 300-mg tablet (B) was more rapidly absorbed than the 300-mg capsule (A), and the 400-mg tablet (E) and the 200-mg capsule (D) were more rapidly absorbed than the 400-mg capsule (C).

The results of a previously reported study indicated that a pilot plant lot of the 300-mg capsule was bioequivalent to the innovator's 300-mg tablet (3). The present study suggested that some change associated with scale-up to commercial production resulted in a less rapidly absorbed dosage form.

Since bioequivalence has been defined as equivalence in both extent and rate of drug absorption (10), it has been concluded that Formulations A and C were bioinequivalent to the innovator's products (B and E) due to their slower absorption rates. Whether this conclusion could be translated to indicate clinical inequivalence could not be determined from these studies. It would be hypothesized, however, that differences in clinical efficacy might be observed when ibuprofen is administered as single doses for the relief of mild to moderate pain.

A more general conclusion resulting from these studies was that the potential exists for bioavailability problems among ibuprofen solid oral dosage forms.

REFERENCES

(1) S. S. Adams, K. F. McCullough, and J. S. Nicholson, *Arch. Int. Pharmacodyn. Ther.*, **178**, 115 (1969).

(2) T. G. Kantor, *Ann. Intern. Med.*, **91**, 877 (1979).

(3) D. L. Simmons, A. A. Legore, P. Picotte, and F. Cesari, *Can. J. Pharm. Sci.*, **15**, 26 (1980).

(4) D. G. Kaiser and G. J. VanGiessen, *J. Pharm. Sci.*, **63**, 219 (1974).

(5) C. M. Metzler, G. L. Elfring, and A. J. McEwen, *Biometrics*, **30**, 562 (1974).

(6) A. Rescigno and G. Segre, in "Drug and Tracer Kinetics," 1st American Edition, Blaisdell, Waltham, Mass., 1966, p. 161.

(7) S. Riegelman and P. Collier, *J. Pharmacokinet. Biopharm.*, **8**, 509 (1980).

(8) J. G. Wagner and E. Nelson, *J. Pharm. Sci.*, **52**, 610 (1963).

(9) J. Neter and W. Wasserman, in "Applied Linear Statistical Models," Irwin, Homewood, Ill., 1974, p. 795.

(10) U.S. Food and Drug Administration, *Fed. Reg.*, **42**, 1635 (1977).

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The Role of Surfactants in the Release of Very Slightly Soluble Drugs from Tablets

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Abstract □ The ability of surfactants to accelerate the *in vitro* dissolution of very slightly soluble drugs has been ascribed to wetting and/or micellar solubilization. Deflocculation as a mechanism to accelerate dissolution has not been investigated. In the present study, the effect of a surfactant on the dissolution kinetics of prednisolone from tablets and the mode of action of the surfactant were investigated. The dissolution of prednisolone at 37° in 0.1 *N* HCl containing different concentrations of the nonionic surfactant, octoxynol 9, followed zero-order kinetics. The rate constant was increased by 15, 150, and 950% when octoxynol was added to the dissolution medium at 0.0039 and 0.032% (~0.5 and 4.0 times the critical micelle concentration) and incorporated into the tablets (for a final concentration of 0.0039%), respectively. The surface tensions of the dissolution media were 71, 35, and 31 dyne/cm for 0, 0.0039, and 0.032% octoxynol, respectively. The largest decrease in surface tension corresponded to the smallest increase in dissolution rate, indicating that wetting was unimportant. The micellar solubilization capacity of octoxynol was much too small to account for the increases in dissolution rate. Microscopic particle size measurements and sedimentation volume determinations showed the pronounced deflocculation of prednisolone by the surfactant. The observed increases in specific surface area at the two octoxynol concentrations were in good quantitative agreement with the increases in dissolution rate according to the Noyes–Whitney equation.

Keyphrases □ Deflocculation—surfactants, release of very slightly soluble drugs, tablets, dissolution kinetics □ Surfactants—release of very slightly soluble drugs, tablets, dissolution kinetics □ Kinetics—dissolution, surfactants, release of very slightly soluble drugs, tablets, deflocculation

The most likely mechanisms by which surfactants could speed up the release of very slightly soluble drugs from tablets are wetting, micellar solubilization, and deflocculation (1). The purpose of the present study was to assess their relative importance in accelerating the dissolution of prednisolone by octoxynol.

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