International Journal of Pharmaceutics, 14 (1983) 59–72
Elsevier Biomedical Press

Ibuprofen tablets: dissolution and bioavailability studies **

J.A. Stead, M. Freeman, E.G. John, G.T. Ward and B. Whiting *

*Roussel Laboratories Ltd., Swindon, Wiltshire, England and * Department of Materia Medica, University of Glasgow, Stobhill General Hospital, Glasgow, Scotland (U.K.)*

(Received March 19th, 1982)
(Modified version received August 2nd, 1982)
(Accepted August 7th, 1982)

Summary

The relative bioavailabilities of a number of oral ibuprofen formulations have been determined in 15 normal healthy volunteers. The formulations comprised tablets from two manufacturers, A and B. The doses from source A were 200, 300 and 400 mg; those from source B were 200 and 400 mg.

For tablets from manufacturer B, the mean of the individual peak plasma levels increased in direct proportion to dose, as did the areas under the curves. Tablets from source A, however, did not show this proportionality and this lack of consistency in relative bioavailabilities was also demonstrated by analysis of variance.

The problems of finding a dissolution procedure which correlated with the in vivo data have been evaluated. Although a simple rotating-basket method, with sink conditions, appeared initially to offer some useful correlations, it failed to adequately separate the most highly bioavailable tablet from the rest of the formulations. The use of an acidic biphasic dissolution system provided the discrimination required and resulted in some satisfactory in vitro–in vivo correlations.

Introduction

Generic bioinequivalence and the correlation of dissolution results with bioavailability data continue to be subjects of debate. The numerous ibuprofen products

** Presented in part by J.A.S. at the 41st International Congress of Pharmaceutical Sciences, Vienna, 7–11 September 1981.

0378-5173/83/0000-0000/$03.00

marketed create a potential bioequivalence problem and in the present study the relative bioavailabilities of 5 formulations from two manufacturers are reported.

Significant differences existed between some of the formulations and the extent to which their in vitro dissolution behaviour was predictive of these differences has been examined. The study of such correlations is important since dissolution testing has become one of the foundations of solid dosage form development and the demand for dissolution data by regulatory bodies is high.

However, in spite of intense activity in the field, there remain surprisingly few drugs for which satisfactory quantitative correlations have been established. These include chloramphenicol (Aguiar et al., 1968; Ogata et al., 1979), aspirin (Levy, 1961; Levy et al., 1965; Gibaldi and Weintraub, 1970), some tetracycline products but not others (Bergan et al., 1973), prednisone (Sullivan et al., 1975), methaqualone (Chemburkar et al., 1976; Gunning et al., 1976) and digoxin products but with certain marked exceptions from the correlations (Fraser et al., 1973; Nyberg et al., 1974; Klink et al., 1974; Ylitalo et al., 1975).

On the other hand there are many examples of drug products showing large differences in dissolution behaviour but little or no difference in bioavailability. Acetaminophen products, for example, showing a 50-fold difference in dissolution, gave only modest changes in bioavailability (Sotiropoulus et al., 1981) and meaningful correlations between absorption parameters and dissolution have been difficult to find for quinidine products (McGilveray et al., 1981), indomethacin (Rowe and Carless, 1981), nitrofurantoin (Mattok et al., 1972), phenylbutazone (Withey et al., 1971), hydrochlorothiazide (Cook, 1971), sulphonamides (Withey et al., 1972; Mattok and McGilveray, 1972) and others. In the case of erythromycin stearate tablets there was no correlation between dissolution and bioavailability although a linear combination of dissolution, disintegration and dissolution/dialysis parameters could be significantly related to appropriate absorption parameters (Stavchansky et al., 1980).

The situation is clearly complex and the reporting of positive or negative in vitro–in vivo correlations is important in order to test the solidity of the foundations for our reliance on dissolution testing as a predictive tool.

Materials and methods

Dosage forms

The formulations examined comprised sugar-coated tablets from two manufacturers, designated A and B. The doses from source A were 200, 300 and 400 mg; those from source B were 200 and 400 mg. The same batches of tablets were used throughout the study and all complied with British Pharmacopoeial requirements for such tablets (Table 1).

In vivo studies

Fifteen (8 male and 7 female) healthy volunteers aged between 18 and 41 years were studied. All were within 10% of their standard body weight for height and

showed no clinically significant abnormality of pre-study biochemical or haematological data.

Each subject received single doses of each of the formulations at no less than weekly intervals, the order of administration being completely randomized by Latin Square design. The subjects refrained from all other medication during the entire course of the study and alcohol was not permitted within 48 h of each individual dosing. Additionally the subjects fasted from 12 h before dosing until 4 h after dosing when a standard lunch was provided.

Before the drug was given, an indwelling intravenous cannula was inserted into a forearm vein and a control blood sample was taken. Patency of the cannula was maintained thereafter by small volumes of heparinized saline. The drug was then given with 100–200 ml water and blood samples were taken at the following times after administration: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 10 h. Apart from the dictates of early frequent sampling, no undue restrictions on physical activity were imposed and the subjects were allowed to carry out normal routine duties.

Plasma assay

A number of methods are available for the measurement of ibuprofen plasma levels. These include gas chromatography of ibuprofen derivatives (Mills et al., 1973; Brooks and Gilbert, 1974; Pettersen et al., 1978; Vangiessen and Kaiser, 1975; Midha et al., 1977) or the free acid (Hoffman, 1977; Hackett and Dusci, 1978) and HPLC procedures (Pitré and Grandi, 1979; Ali et al., 1981).

For the present study, which involved the analysis of 900 plasma samples in duplicate, an automated version of the HPLC method developed by Ward et al. (1982) for tiaprofenic acid was used.

In common with the other analytical methods cited (the exceptions being Mills et

TABLE I

IBUPROFEN TABLETS—COMPLIANCE WITH BRITISH PHARMACOPOEIAL REQUIREMENTS

	A200	A300	A400	B200	B400	BP limits
Content of ibuprofen (% of stated amount)	104.4	96.0	95.7	97.8	99.7	95–105
Identity	←	←	satisfies test		→	→
Related compounds (TLC)	←	←	satisfies test		→	→
Mean tablet weight [a] (mg)	481	730	803	493	1025	–
Uniformity of weight [a] (as % coefficient of variation)	2.0	1.9	2.2	1.8	2.2	–
Disintegration time, (min) (range)	6 (3–6)	22 (5–22)	17 (6–17)	16 (4–16)	16 (6–16)	60

[a] Not an official requirement for coated tablets.

al. (1973) and Pettersen et al. (1978); the latter working with urine) the specificity of the assay for ibuprofen has not been examined. Mills et al. (1973) showed that ibuprofen appears mainly in unchanged form in human plasma (metabolites representing 15% or less of the ibuprofen concentration at the peak plasma level) and it is considered that any lack of specificity in the assay would have no effect on the conclusions reached regarding bioavailability of the products.

Apparatus

A liquid chromatographic pump [1] and autosampler [2], fitted with a 20 μl loop, was connected to a detector [3], operated at a wavelength of 220 nm and a range of 0.02 aufs, and interfaced with a computing integrator [4].

Column

A 100 × 5 mm i.d. column, packed with ODS-Hypersil [5] was used at ambient temperature.

Mobile phase

A mixture of 67% methanol and 33% water with the pH adjusted to 3 with 0.1 N sulphuric acid at a flow rate of 1 $ml \cdot min^{-1}$ was used.

Internal standard

A solution of butyl-*p*-hydroxybenzoate at a concentration of 0.1 $\mu g \cdot ml^{-1}$ in chloroform was used.

Preparation of standard curves

Aqueous solutions were prepared containing 10, 20, 50, 100 and 200 $\mu g \cdot ml^{-1}$ ibuprofen. 20 μl aliquots of each of these were diluted to 200 μl with human drug-free plasma to give plasma standards containing 1, 2, 5, 10 and 20 $\mu g \cdot ml^{-1}$.

Extraction of samples

To a Dreyer tube [6] were added 200 μl of plasma sample and 200 μl of 6% trichloroacetic acid. The contents of the tube were mixed [7] for 10 s and 200 μl of internal standard solution was added. After further mixing for 1 min the tube was centrifuged [8] for 2 min. The aqueous phase was discarded and 150 μl of the chloroform layer was transferred to a low volume autosampler vial. The chloroform

[1] Magnus P4000 pump; Magnus Scientific, Cheshire, U.K.
[2] Magnus M7100 autosampler; Magnus Scientific, Cheshire, U.K.
[3] Pye-Unicam LC-UV; Pye-Unicam, Cambridge, U.K.
[4] PEP I data system; Perkin-Elmer, Beaconsfield, U.K.
[5] Shandon Products, Cheshire, U.K.
[6] Poulten, Self and Lee, Wickford, Essex, U.K.
[7] Vortex mixer; Hook and Tucker, New Addington, Croydon, U.K.
[8] Eppendorf 5412; Netheler and Hinz GmbH, 2000 Hamburg 63. The low volume adaptors of the centrifuge were drilled out to accept the Dreyer tubes.

was evaporated to dryness under a gentle stream of nitrogen and the residue was redissolved in 150 μl of mobile phase.

Quantitation

Spiked plasma extracts were chromatographed and standard curves were constructed by plotting the ratios of ibuprofen peak areas to internal standard peak areas versus the concentration of drug. Calibration standards were chromatographed each day when unknown samples were analyzed. The concentrations of ibuprofen in the unknown samples were determined by comparison of the peak area ratios to the standard curve obtained that day.

In vitro studies

Method 1

USP XX rotating-basket method at 100 rpm was employed using 900 ml of phosphate buffer solution at pH 6.9 [9], maintained at 37°C. At this pH the total solute concentration from the 400 mg tablets remained below 10% of the saturation solubility, thus satisfying requirements for sink conditions. The dissolution results are the mean of 12 determinations. The amounts dissolved at appropriate time intervals were determined spectrophotometrically at 263.5 nm. Seven or more data points were used to characterize the curves.

Method 2

The rotating-basket apparatus of the USP XX was again employed, operating at 200 rpm but the dissolution medium comprised 500 ml of 0.1 N hydrochloric acid, in which the basket was immersed, with an overlying layer of 400 ml of HPLC grade *n*-hexane to provide sink conditions. The solubility of the drug in 0.1 N HCl is ~ 0.006% w/v and in *n*-hexane is in excess of 5% w/v. The apparatus was maintained at 37°C and the interface between the aqueous and organic layer was agitated by means of a stirrer [10] attached 2 cm above the basket, such that the lower leading edges of the blades penetrated 2 mm into the aqueous phase. The amounts transferred to the hexane layer at appropriate time intervals were determined spectrophotometrically at 264 nm. Results quoted are the means of 6 determinations.

Results and discussion

Analytical method

The spiked plasma standards produced linear calibration curves passing through the origin. The method was assessed by analyzing a series of 36 unknown spiked plasma samples, prepared by others and coded numerically over the ibuprofen

[9] Sorensen's phosphate; Scientific Tables, Documenta Geigy 7th Edn., Geigy Pharmaceuticals, Macclesfield, U.K., 1970, p. 280.

[10] Stainless steel, 4-bladed impeller, 45 mm diameter with the blades inclined at 45°.

TABLE 2

RECOVERY AND REPRODUCIBILITY OF IBUPROFEN PLASMA ASSAY

Amount added ($\mu g \cdot ml^{-1}$) (n = 6)	Mean amount found ($\mu g \cdot ml^{-1}$)	Recovery (%)	Coefficient of variation (%)
0	0		
0.99	0.96	97.1	8.5
3.08	2.93	95.2	8.8
9.69	9.50	98.0	6.6
18.6	17.6	94.7	5.9
30.1	29.3	97.3	2.8

concentration range of 0–30 $\mu g \cdot ml^{-1}$. A summary of the results is shown in Table 2 which confirms the accuracy and reproducibility of the method, which was sufficiently rapid to permit 60 determinations in a 24 h period.

In vivo studies

Fig. 1 shows the mean ibuprofen plasma levels versus time for each of the formulations. The approximate doubling of area under the curve and peak plasma level (Cp_{max}) for tablet B400 when compared to B200 is immediately apparent. No

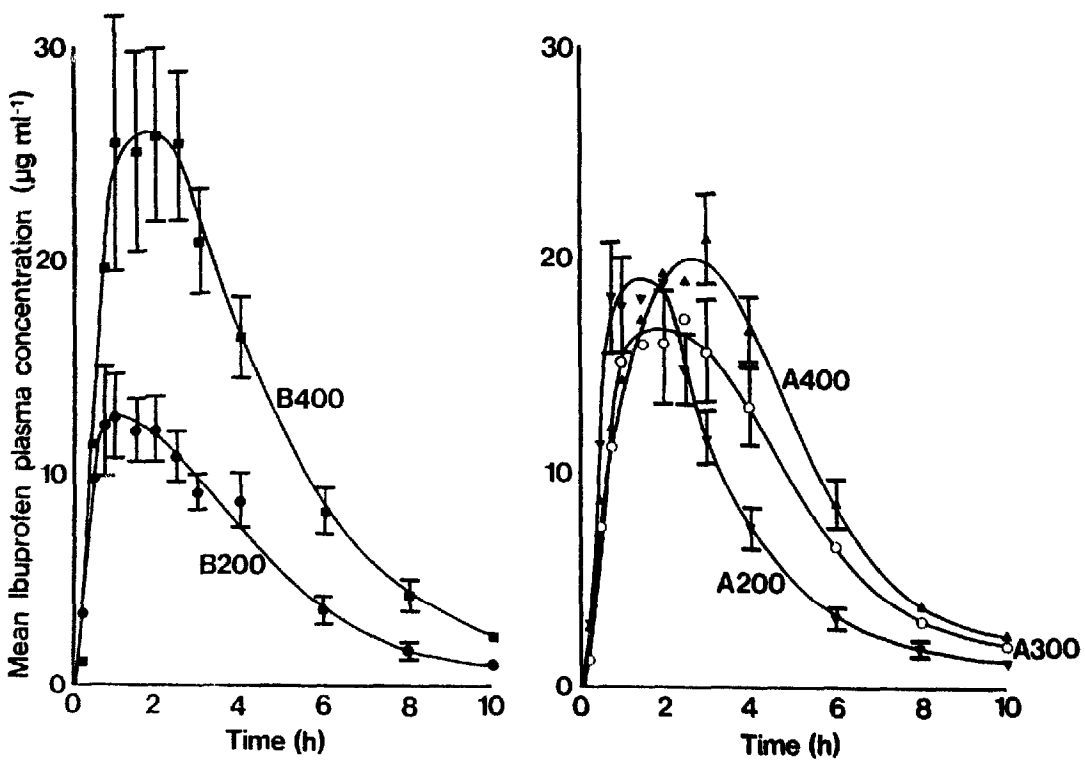

Fig. 1. Mean ibuprofen plasma levels. Vertical lines indicate standard error of the mean values.

TABLE 3

COMPARATIVE BIOAVAILABILITY OF IBUPROFEN FORMULATIONS

Formulation	$AUC_{0-\infty}$ ($\mu g \cdot h \cdot ml^{-1}$)			Cp_{max} ($\mu g \cdot ml^{-1}$)			t_{peak} (min)	
	Mean	Mean (normalized to 100 mg dose)	S.D.	Mean	Mean (normalized to 100 mg dose)	S.D.	Mean	S.D.
A200	76.0	38.0	14.0	27.0	13.5	5.5	82.5	34.7
A300	93.6	31.2	14.6	20.1	6.7	3.4	101.7	56.4
A400	113.6	28.4	7.0	25.6	6.4	1.9	148.7	60.3
B200	63.0	31.5	8.7	19.0	9.5	3.2	116.9	96.5
B400	128.8	32.2	11.5	36.4	9.1	4.7	124.3	81.5

such proportionality is evident for the tablets from manufacturer A and the similarities in Cp_{max} values are surprising.

Model-independent pharmacokinetic parameters of the products are presented in Table 3 as well as some values normalized to a 100 mg dose, where appropriate, for comparative purposes. Values of area under the curve to infinity ($AUC_{0-\infty}$) were estimated by the trapezoidal rule and Cp_{max} and times to Cp_{max} (t_{peak}) were read directly from the data for each subject. It is noteworthy that Cp_{max} for A200 is higher than any Cp_{max} other than that for B400. Further separation of A200 from the rest of the formulations is evidenced by its higher normalized $AUC_{0-\infty}$ and lower t_{peak} value than for the other tablets.

After normalizing each mean $AUC_{0-\infty}$ and Cp_{max} for dose, statistical analyses were performed by both parametric and non-parametric two-way analyses of variance. Significant differences ($P < 0.05$) existed between A200 and A300 and between A200 and A400 in terms of $AUC_{0-\infty}$. The large numerical difference in normalized Cp_{max} for A200 and the rest of the formulations just failed to reach a significant level. Similarly there were no significant differences in t_{peak}.

Using non-linear least-squares regression analysis, mean plasma concentration-time results were fitted to a one-compartment model and the data for

TABLE 4

MEAN KINETIC PARAMETERS DERIVED FROM ANALYSIS OF POOLED DATA

Preparation and dose	A ($\mu g \cdot ml^{-1}$)	k_e (h^{-1})	B ($\mu g \cdot ml^{-1}$)	k_a (h^{-1})
A200	33.3	0.35	49.4	2.31
A300	47.5	0.33	52.1	0.99
A400	60.5	0.33	66.9	0.86
B200	24.4	0.32	27.9	1.76
B400	56.0	0.32	73.6	1.45

each formulation were characterized by the biexponential equation

$$Cp(t) = Ae^{-k_e t} - Be^{-k_a t}$$

where A and B are the coefficients of the exponential terms, k_e is the first-order elimination rate constant and k_a is the apparent first-order absorption rate constant. The values of these 4 parameters are presented in Table 4.

The values of k_e show close similarity between formulations with a mean value of 0.33 h^{-1}, in good agreement with the mean value in volunteers found by Collier et al. (1978). In contrast, k_a values vary widely for each formulation decreasing from 2.31 h^{-1} for A200 to 0.86 h^{-1} for A400.

In vitro–in vivo correlations

Dissolution results using pH 6.9 buffer (Method 1) are presented in Fig. 2. Inspection of these data shows some possibilities of in vitro–in vivo correlations since A200 was found to dissolve more rapidly than A300 and A400. A negative aspect, however, is that the dissolution method has effectively separated B200 and B400 which showed linearity of pharmacokinetic parameters, i.e. the dissolution procedure has perceived a manufacturing or formulation difference which has no influence on bioavailability.

In order to investigate possible correlations, the mean plasma concentration–time curves were converted into percentage absorbed–time plots using the method, appropriate to one-compartment model systems, derived by Wagner and Nelson (1963). The problems of using data from the mean results rather than from

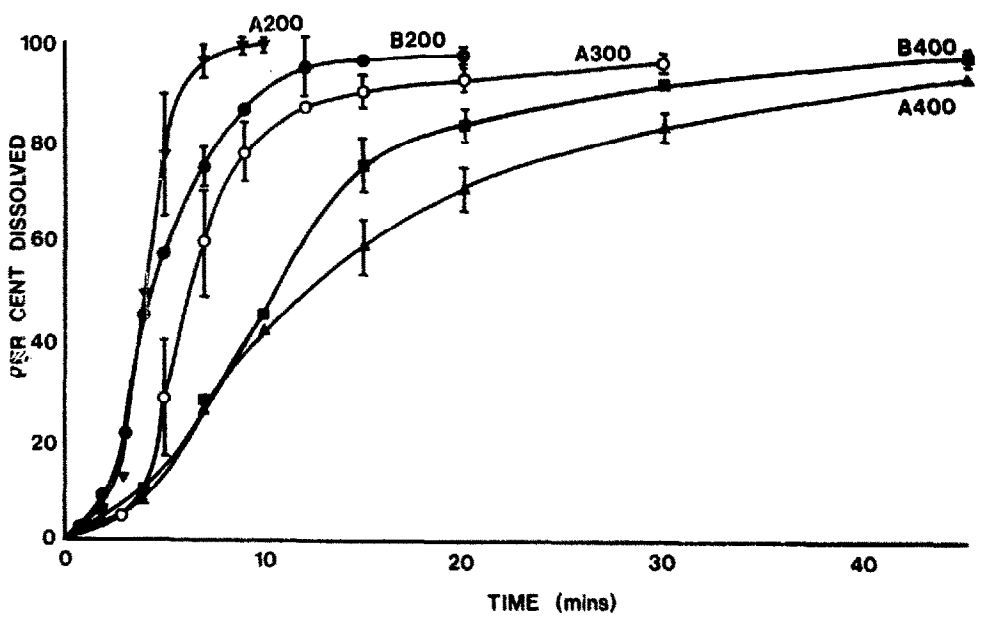

Fig. 2. Dissolution of ibuprofen tablets using Method 1. Mean (n = 12) curves in 900 ml pH 6.9 buffer, USP rotating-basket at 100 rpm. Representative standard deviations are indicated by the vertical bars.

individuals has been discussed by Levy and Hollister (1964) and Riegelman and Upton (1979). In the present case both the individual results and the mean data for each formulation showed first-order kinetics. Consequently percent absorbed–time data derived from the mean plasma concentration–time data was appropriate for comparison with the dissolution results, which also showed apparent first-order kinetics.

An examination of the in vitro and in vivo data indicated that the best correlation existed between percent absorbed at time t and percent dissolved at t/5 as shown in Fig. 3. The relationship is highly significant ($P < 0.001$). However, correlation of the pharmacokinetic parameters of Table 3 with the dissolution results give little success, other than for t_{peak} versus time for 50% dissolution ($t_{50\%}$) which shows a low order of significance ($P < 0.1$). The significance can be increased to a higher level ($P < 0.01$) only if B200 is omitted from consideration.

A critical evaluation of the data shown in Fig. 3 reveals the relationship to be largely fortuitous. Following Levy et al. (1965), intensity factors (I) for the dissolution process as compared to in vivo absorption were determined for each formula-

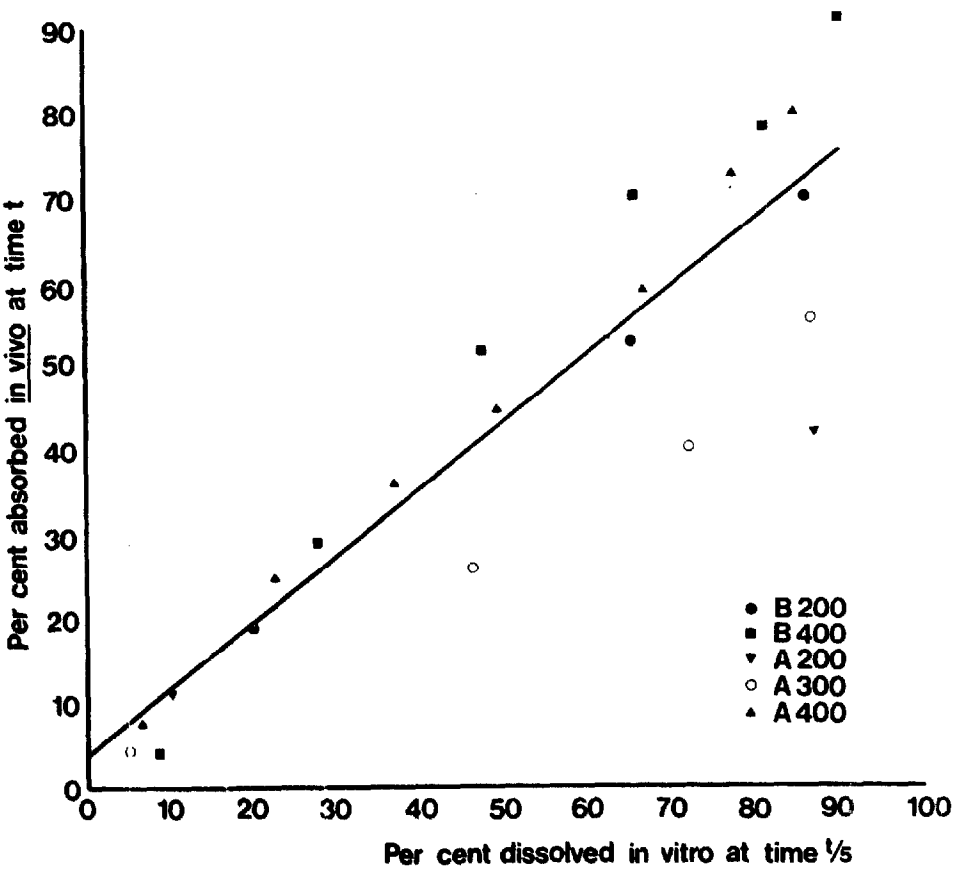

Fig. 3. Plot of percent of dose of ibuprofen absorbed at time t after drug administration versus percent dissolved in vitro at time t/5 using Method 1. Statistically significant, $P < 0.001$.

tion from the ratio of the rate constant for dissolution: rate constant for absorption. The inadequacies of the dissolution test (Method 1) are shown by the wide variation in I values which were 17.4, 17.2, 5.0, 9.9 and 5.2 for A200, A300, A400, B200 and B400, respectively. The apparently good correlation of the data of Fig. 3 is due to the close similarity in I-values for A400 and B400 and that their slower rates of dissolution permit far more data points to be used than for the other tablets, which consequently are unable to appreciably reduce the significance of the correlation. Caution is necessary in accepting the significance of plots of this type unless sufficient formulations have been adequately examined to validate the procedure. The convenient omission of formulations from correlations or the consideration of only the best correlations, as sometimes reported, may be misleading.

In terms of normalized $AUC_{0-\infty}$, A200 is some 20% more bioavailable than the rest of the formulations for which values of this parameter are closely similar. Consequently the need for a dissolution procedure which would discriminate A200 from the rest was apparent. Such differentiation was achieved using Method 2, involving dissolution in acid and transfer to an overlying organic phase, the results being shown in Fig. 4.

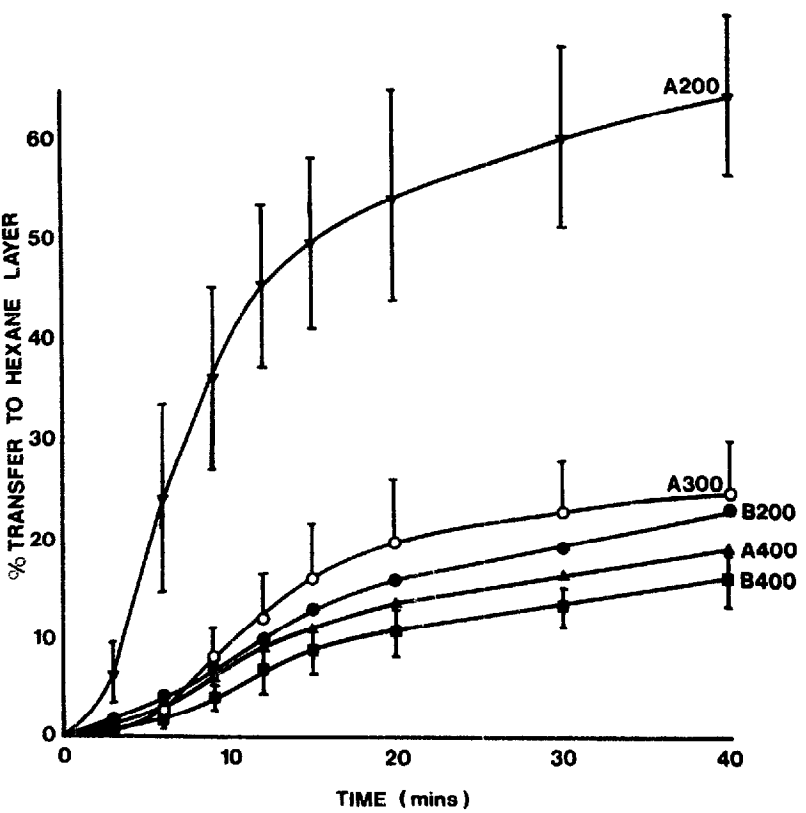

Fig. 4. Dissolution of ibuprofen tablets using Method 2. Mean (n = 6) curves of percent of dose of ibuprofen transferred to hexane layer after dissolution in 0.1 N hydrochloric acid. Representative standard deviations are indicated by the vertical bars.

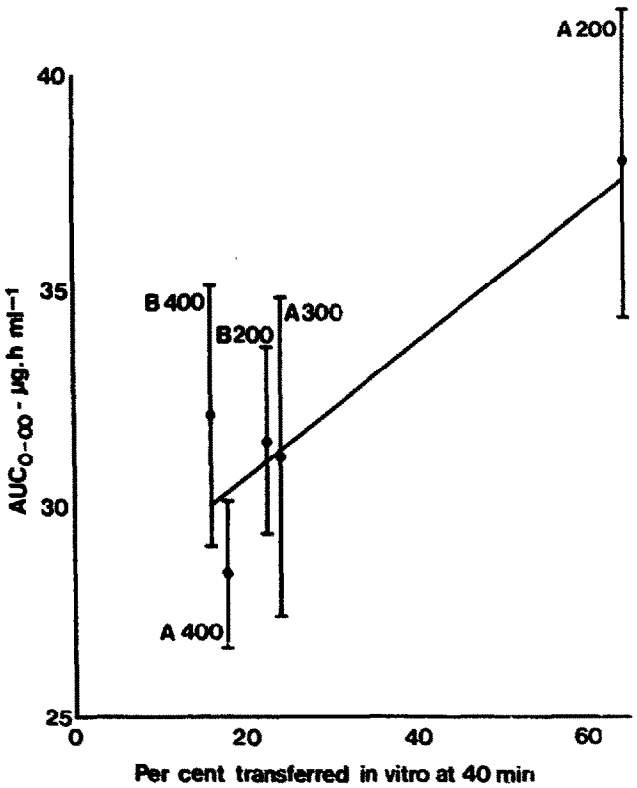

Fig. 5. Plot of normalized $AUC_{0-\infty}$ versus percent of dose of ibuprofen transferred to hexane layer at 40 min, following dissolution in 0.1 N hydrochloric acid. Statistically significant, $P < 0.05$. Vertical lines indicate standard error of the means.

It was found, by selecting a period of 40 min, that a relationship existed between percent transferred at this time and the normalized pharmacokinetic parameters as shown in Figs. 5 and 6. Unfortunately the extent of dissolution and transfer to the organic phase was too low for 4 of the formulations to seek point-to-point correlations of in vitro and in vivo data, of the type shown in Fig. 3.

Examination of the contents of the basket subsequent to a Method 2-type dissolution experiment showed the presence of tablet aggregates for all formulations other than A200 which suggests that the lower relative bioavailability of these tablets when compared to A200 was due to deaggregation problems in acidic media such as the stomach contents.

There is little doubt that with appropriate variation in dissolution methodology, e.g. pH of the medium, presence of surfactants, stirrer speed, etc., the correlations shown in Figs. 5 and 6 could be improved. In particular, modifications which would increase the dissolution rates of B200 and B400 relative to A300 and A400 would need to be sought since the former pair of tablets showed higher Cp_{max} and k_a values than the latter formulations. However, the extent to which further refinements are desirable is a matter for debate. For the present formulations the use of an acidic dissolution medium was the key to a broad differentiation between A200 and the

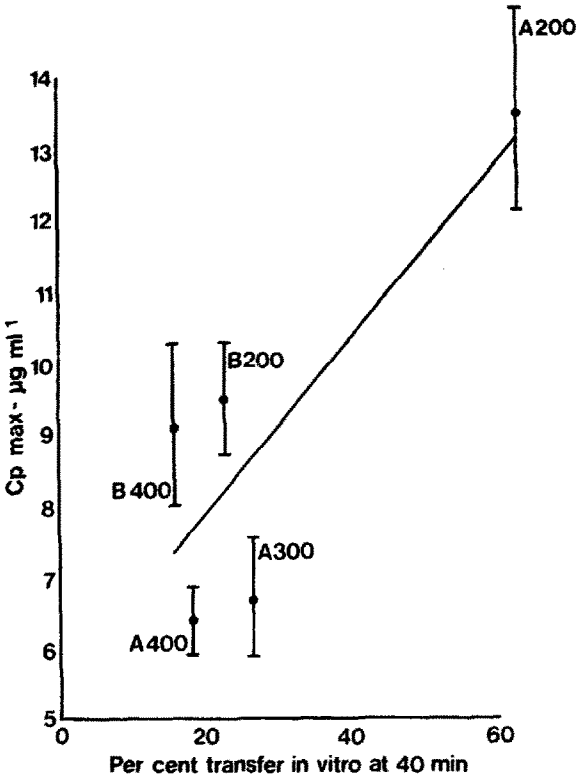

Fig. 6. Plot of normalized Cp_{max} versus percent of dose of ibuprofen transferred to hexane layer at 40 min, following dissolution in 0.1 N hydrochloric acid. Statistically significant, $P < 0.1$. Vertical lines indicate standard error of the means.

rest; however, there is no reason to believe that the same dissolution procedure would be appropriate if tablets from a third manufacturer were to be examined. This is an aspect of concern regarding the setting of compendial standards for the dissolution of drug products.

That dissolution results can give misleading information is demonstrated by the data obtained using Method 1 which showed: (a) a marked differentiation between B200 and B400 which were bioequivalent after normalizing for dose; and (b) a rapid dissolution rate for A300, almost approaching B200 and A200, which, in common with the slowly dissolving A400, gave low Cp_{max} and k_a values in vivo.

In conclusion, with the present state of knowledge, there is little to indicate that a general dissolution test based on drug solubility considerations and predictive of the response in man, is likely to become available in the foreseeable future and the continuing need for bioavailability studies in man is clear. Additionally the need to critically evaluate the data used to obtain in vitro–in vivo correlations has been demonstrated since it is possible to obtain fortuitous correlations if few formulations are examined or only the 'best fit' data are considered.

Acknowledgements

We are indebted to P. Cole, L. Przeleski and A. Mundy for technical assistance.

References

Aguiar, A.J., Wheeler, L.M., Fusari, S. and Zelmer, J.E., Investigation of physical and pharmaceutical factors involved in drug release and availability from chloramphenical capsules. J. Pharm. Sci., 57 (1968) 1844–1850.

Ali, A., Kazmi, S. and Plakogiannis, F.M. High pressure liquid chromatographic determination of ibuprofen in plasma. J. Pharm. Sci., 70 (1981) 944–945.

Bergan, T., Oydvin, B. and Lunde, I., Biological availability and in vitro release from oral oxytetracycline and tetracycline preparations. Acta Pharmacol. Toxicol., 33 (1973) 138–156.

Brooks, C.J. and Gilbert, M.T., Studies of urinary metabolites of ibuprofen by gas liquid chromatography–mass spectrometry. J. Chromatogr., 99 (1974) 541–551.

Chemburkar, P.B., Smyth, R.D., Buehler, J.D., Shah, P.B., Joslin, R.S., Polk, A. and Reavey-Cantwell, N.H., Correlation between dissolution characteristics and absorption of methaqualone from solid dosage forms. J. Pharm. Sci., 65 (1976) 529–533.

Collier, P.S., D'Arcy, P.F., Harron, D.W.G. and Morrow, N., Pharmacokinetic modelling of ibuprofen. Br. J. Clin. Pharmacol., 5 (1978) 528–530.

Cook, D., Panel discussion on case histories in bioavailability of drugs: Canadian experience. In Brodie, B.B. and Heller, W.M. (Eds.), Bioavailability of Drugs, Karger, New York, 1972, pp. 193–194.

Fraser, E.J., Leach, R.H., Poston, J.W., Bold, A.M., Culank, L.S. and Lipede, A.B., Dissolution and bioavailability of digoxin tablets. J. Pharm. Pharmacol., 25 (1973) 968–973.

Gibaldi, M. and Weintraub, H., Quantitative correlation of absorption and in vitro dissolution kinetics of aspirin from several dosage forms. J. Pharm. Sci., 59 (1970) 725–726.

Gunning, S.R., Kendall, M.J., Mitchard, M., Stead, J.A. and Williams, M.E., The effect of some formulation variables on the bioequivalence of methaqualone preparations. J. Clin. Pharm., 1 (1976) 189–200.

Hackett, L.P. and Dusci, L.J., Gas–liquid chromatographic determination of ibuprofen in human plasma. Clin. Chim. Acta., 87 (1978) 301–303.

Hoffman, D.J., Rapid GLC determination of ibuprofen in serum. J. Pharm. Sci., 66 (1977) 749–750.

Klink, P.R., Poust, R.I., Colaizzi, J.L. and McDonald, R.H., Jr., Bioavailability and dissolution properties of two commercial digoxin tablets. J. Pharm. Sci., 63 (1974) 1231–1234.

Levy, G., Comparison of dissolution and absorption rates of different commercial aspirin tablets. J. Pharm. Sci., 50 (1961) 388–392.

Levy, G., Leonards, J.R. and Procknal, J.A., Development of in vitro dissolution tests which correlate quantitatively with dissolution rate-limited drug absorption in man. J. Pharm. Sci., 54 (1965) 1719–1722.

Levy, G. and Hollister, L.E., Inter- and intrasubject variations in drug absorption kinetics. J. Pharm. Sci., 53 (1964) 1446–1452.

Mattok, G.L., Hossie, R.D. and McGilveray, I.J., In vivo: in vitro studies of nitrofurantoin tablets. Can. J. Pharm. Sci., 7 (1972) 84–87.

Mattok, G.L. and McGilveray, I.J., Comparison of bioavailabilities and dissolution characteristics of commercial tablet formulations of sulfamethiazole. J. Pharm. Sci., 61 (1972) 746–749.

McGilveray, I.J., Midha, K.K., Rowe, M., Beaudoin, N. and Chanette, C., Bioavailability of 11 quinidine formulations and pharmacokinetic variation in humans. J. Pharm. Sci., 70 (1981) 524–529.

Midha, K.K., Cooper, J.K., Hubbard, J.W. and McGilveray, I.J., A rapid and simple GLC procedure for determinations of plasma concentrations of ibuprofen. Can. J. Pharm. Sci., 12 (1977) 29–31.

Mills, R.F.N., Adams, S.S., Cliffe, E.E., Dickinson, W. and Nicholson, J.S., Metabolism of ibuprofen. Xenobiotica, 3 (1973) 589–598.

Nyberg, L., Andersson, K. and Bertler, A., Bioavailability of digoxin from tablets. III. Availability of digoxin in man from preparations with different dissolution rates. Acta. Pharm. Suec., 11 (1974) 471–492.

Ogata, H., Shibazaki, T., Inoue, T. and Ejima, A., Dissolution systems for chloramphenicol tablet bioavailability. J. Pharm. Sci., 68 (1979) 712–715.

Pettersen, J.E., Ulsaker, G.A. and Jellum, E., Studies on the metabolism of ibuprofen by gas chromatography and mass spectrometry. J. Chromatogr., 145 (1978) 413–420.

Pitré, D. and Grandi, M., Rapid determination of ibuprofen in plasma by high performance liquid chromatography. J. Chromatogr., 170 (1979) 278–281.

Riegelman, S. and Upton, R.A., In vitro and in vivo bioavailability correlation. In Prescott L.F. and Nimmo W.S. (Eds.), Drug Absorption: Proceedings of the 1979 Edinburgh International Conference, Adis, Balgowlah, Australia, 1981, pp. 297–312.

Rowe, J.S. and Carless, J.E., Comparison of the in vitro dissolution behaviour of various indomethacin formulations with their in vivo bioavailability. J. Pharm. Pharmacol., 9 (1981) 561–564.

Sotiropoulus, J.B., Deutsch, T. and Plakogiannis, F.M., Comparative bioavailability of three commercial acetominophen tablets. J. Pharm. Sci., 70 (1981) 422–424.

Stavchansky, S., Doluisio, J.T., Martin, A., Martin, C., Cabana, B., Dighe, S. and Loper, A. Correlation of in vivo bioavailability of erythromycin stearate tablets with in vitro tests. J. Pharm. Sci., 69 (1980) 1307–1310.

Sullivan, T.J., Sakmar, E., Albert, K.S., Blair, D.C. and Wagner, J.G., In vitro and in vivo availability of commercial prednisone tablets. J. Pharm. Sci., 64 (1975) 1723–1725.

Vangiessen, G.J. and Kaiser, D.G., GLC determination of ibuprofen enantiomers in biological specimens. J. Pharm. Sci., 64 (1975) 798–801.

Wagner, J.G. and Nelson, E., Per cent absorbed time plots derived from blood level and or urinary excretion data. J. Pharm. Sci., 52 (1963) 610–611.

Ward, G.T., Stead, J.A. and Freeman, M., A rapid and specific method for the determination of tiaprofenic acid in human plasma by high-performance liquid chromatography. J. Liq. Chromatgr., 5 (1982) 165–174.

Withey, R.J., Feng, H., Cook, D., Van Petten, G.R. and Lettau, H.F., The physiologic availability of solid dosage forms of phenylbutazone. II. Correlation of in vivo physiologic availability and in vitro dissolution parameters. J. Clin. Pharmacol., 11 (1971) 187–196.

Withey, R.J., Van Petten, G.R. and Lettau, H.F., Physiological availability and metabolism of sulphonamides. III. Triple sulfa. J. Clin. Pharmacol., 12 (1972) 190–195.

Ylitalo, P., Wilen, G. and Lundell, S., Bioavailability of digoxin tablets in relation to their dissolution in vitro. J. Pharm. Sci., 64 (1975) 1264–1266.