Drug Development and Industrial Pharmacy, 23(10), 987-992 (1997)

RESEARCH PAPER

Relationship Between Dissolution Rate and Bioavailability of Sustained-Release Ibuprofen Capsules

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ABSTRACT

Dissolution studies of three marketed brands of ibuprofen sustained-release (SR) capsules were conducted on USP XIX dissolution apparatus 1, using buffers simulating the gastrointestinal tract (GIT) pHs. The products showed almost identical drug release pattern in dissolution studies. A single-dose crossover oral bioavailability study revealed statistically significant differences in C_{max}, T_{max}, AUC and percent bioavailability values among the SR products but no such differences are evident in the $t_{1/2a}$, K_a, $t_{1/2e}$, and K_e. Retard quotient values were used to evaluate the sustained-release nature of the products. Statistical moment parameters such as MRT, MAT, and MDT were related with the dissolution parameters. Statistically significant correlations were observed between $MRT_{in\ vitro}$ and $MRT_{in\ vivo}$ or $MDT_{in\ vivo}$; $T_{50\%}$ and T_{max}; and $T_{90\%}$ and C_{max} or AUC_0^{12}. The determination of $MRT_{in\ vitro}$, $T_{50\%}$, and $T_{90\%}$ may be useful as quality control parameters to which each batch of the ibuprofen SR products could be submitted.

INTRODUCTION

Ibuprofen, a propionic acid derivative, is widely prescribed in the treatment of osteoarthritis, rheumatoid arthritis, and mild to moderate pain (1), either alone or in combination with other analgesic-antipyretic drugs. Sustained-release (SR) products of ibuprofen for once- or twice-daily administration have been introduced in the Indian market, and are now popular with prescribers. Ibuprofen possesses low aqueous solubility and poor wettability characteristics (2,3), and bioavailability problems are a distinct possibility (4). Liu et al. (5) have reported good correlation between percent dissolution and *AUC* for Fenbid® SR capsules of ibuprofen, and two-layered SR tablets of ibuprofen showed good correlation between cumulative percent

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absorbed and cumulative percent dissolved (6). Correlation was unsatisfactory for the ibuprofen SR capsules prepared using cellulose derivatives as excipients (7), giving rise to the impression that in vitro–in vivo correlation studies of ibuprofen SR products can lead to important and fruitful data. Kottke and Rhodes have suggested that prolonged-release products may be an especially fruitful area for an in vitro–in vivo correlation type of study (8). If a correlation can be drawn between in vitro dissolution and some parameter of bioavailability, then the relatively simple procedure of monitoring the dissolution profile should permit the prediction of in vivo availability (9). The logic and interest behind the correlation is the use of in vitro values to evaluate different lots of a drug product as a quality control check to ensure a desired physiologic performance, and as a developmental tool for a series of dosage forms to achieve a desired in vivo performance goal. A number of different in vivo parameters have been recently described in the literature for correlating with the standard in vitro parameters for cephadrine, piroxicam, perphenazine, and nitrofurantoin (10–12). The present work describes investigations conducted to establish a correlation between in vitro ($T_{x\%}$ and *MRT*) and in vivo (*MRT, MDT, MAT,* T_{max}, C_{max}, and *AUC*) parameters of ibuprofen SR capsules marketed in India.

MATERIALS AND METHODS

Materials

The SR capsules (300 mg) examined were gift samples of three brands S_A, S_B, and S_C of ibuprofen (Inflakil® [Targof], Inflapen® [Allenburys] and Ibubid® [Natco], respectively) and a conventional tablet, CT (Brufen® 600 mg [Boots]). Ibuprofen I.P. was generously supplied by Sol Pharmaceuticals, Hyderabad. All other chemicals used were AR grade.

In Vitro Dissolution Studies

Dissolution studies were conducted on a USP XIX dissolution apparatus 1. The capsule shell material interfered with the spectrophotometric assay of ibuprofen. Hence, one capsule was opened and its contents put inside the USP basket, wrapped with a nylon sieve (200 mesh). The basket was dipped into 500 ml of prewarmed (37°C) dissolution medium of pH 1.2 and agitated at 100 rpm. After 0.5 hr, the basket assembly was raised gently and the fluid in the basket assembly was completely drained. The basket containing the pellets was washed with 10 ml of distilled water and drained well. The drained fluid was mixed with the dissolution fluid and 5 ml of the dissolution medium was collected through a polyethylene tube packed tightly with glass wool at the lower end. The dissolution medium was replaced with fresh prewarmed (37°C) dissolution medium (500 ml) of pH 1.2 and agitated at 100 rpm. After the expiry of 0.5 hr, the sampling process was repeated and the dissolution medium was replaced with phosphate buffer of pH 4.6. The process of changing the dissolution medium was repeated at the end of 1.5 and 2 hr with phosphate buffer of pH 6.0, at the end of 2.5, 3.5, and 4.5 hr with phosphate buffer of pH 7.0, and at the end of 5.5, 6.5, 7.5, and 8.5 hrs with a phosphate buffer of pH 7.4. The samples were diluted suitably with respective dissolution fluid and their absorbances were read on a UV/VIS Jasco-7800 spectrophotometer at 221 nm against blank dissolution fluid. The pHs of the dissolution medium were selected to simulate in vivo conditions, and the periodic change of the whole dissolution medium ensured sink conditions in the dissolution studies. Dissolution of the ibuprofen tablets was determined using USP XXI methodology, which employs a basket rotating at 150 rpm in 900 ml of phosphate buffer of pH 7.2. The specification for tablets was *Q* not less than 50% at 30 min.

Bioavailability Studies

In the bioavailability study, seven informed volunteers (four males and three females, age 24.3 ± 0.61 years; weight 56.7 ± 4.5 kg) were screened for normal physiological functions and fasted for 12 hr. The subjects refrained from all medication for 15 days prior to and during the course of the study. The subjects took a light breakfast (three lightly buttered pieces of toast, one banana, and 50 ml skimmed milk) 30 min prior to ingestion of ibuprofen formulations (one conventional tablet or two SR capsules equivalent to 600 mg of ibuprofen) with 100 ml of water in a single-dose crossover study. Five milliliters of blood was withdrawn from a cubital vein with a heparinized syringe at 0, 1, 2, 3, 4, 6, 8, 12, and 24 hr for SR formulations and 0, 1, 1.5, 2, 3, 4, 6, 8, and 12 hr for the conventional formulation. Blood samples were centrifuged and the separated plasma samples were stored at −20°C until analysis. Volunteers were provided with a morning snack (two biscuits and one banana) 3 hr after breakfast, and a standard vegetarian lunch 5 hr after breakfast. Plasma samples were assayed in a UV spectrophotom-

eter by the modified method of Shingte et al. (13). One milliliter of plasma was acidified with 0.2 ml of perchloric acid (70%) and extracted with 8 ml of chloroform for 10 min. The organic layer was separated and treated with 0.5 g of anhydrous sodium sulphate and kept for 15 min with occasional shaking. The chloroform extract was decanted completely into a small, dry, conical flask and evaporated at 55°C on a waterbath; 2 ml of phosphate buffer (pH 7.2) was added to it and shaken to dissolve the extracted drug. The absorbance was read at 221 nm against zero hour plasma carried through the same procedure. Plasma ibuprofen concentration was estimated from a standard calibration curve ($r = 0.997$) prepared from pooled unmedicated plasma spiked with known concentrations of ibuprofen.

RESULTS AND DISCUSSION

In vitro dissolution profiles of ibuprofen from SR capsules showed almost identical rate and extent of drug release pattern (Fig. 1). Products S_A, S_B, and S_C showed about 5, 4, and 6% drug release, respectively, at the end of 2.5 hr in acidic pHs (pH 1.2 for 1 hr, pH 4.6 for 0.5 hr, and pH 6.0 for 1 hr). The initial low level of drug release from the SR pellets is both due to uniformly coated drug powder with acid-resistant polymer and the practically insoluble nature of the drug in acidic pHs. The extent of retardation of drug release depends on the dissolution medium and the coating-to-core ratio (14). The lag time in achieving a constant release was related to the time necessary for the saturation of the capillaries by the penetrating liquid, whereas the rate of release was influenced by the pore volume effectively penetrated by water (15).

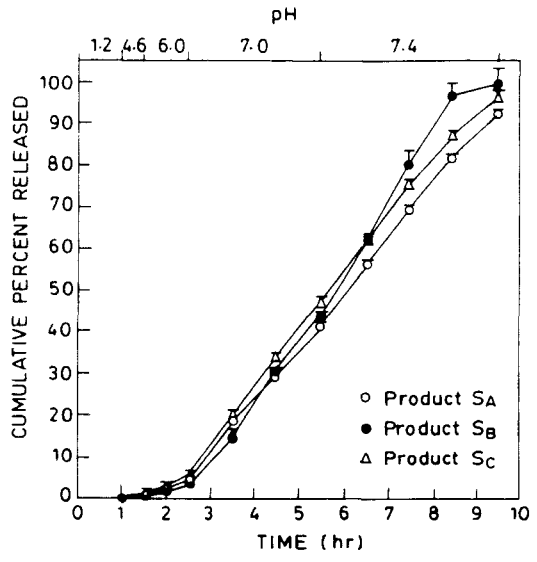

Figure 1. In vitro dissolution profiles of ibuprofen from marketed SR capsules.

At the end of 5.5 hr, the amount of drug released from products S_A, S_B, and S_C was 42, 44, and 48%, respectively, while the same products at 9.5 hr released 92.6, 97.62, and 96.1% of ibuprofen, respectively. On changing the dissolution medium to pH 7.0 and 7.4, the drug release is controlled by a combination of diffusion, polymer erosion, and leaching or pore formation (16,17). The polymer coating becomes thinner and less rigid because of rapid erosion of the polymer, and then the medium penetrates into the film more rapidly, thereby increasing drug release. The release profiles of the SR products indicate a zero-order release pattern. A basic performance requirement of SR delivery systems is that they should release the drug in vivo at a predictable rate. Ideally, the rate should be zero-order and uniform in both gastric and intestinal media (18–20). The ibuprofen conventional tablet readily passed the USP Q value of not less than 50% at 30 min.

Pharmacokinetic parameters derived from the plasma ibuprofen data are summarized in Table 1. The mean plasma profiles of the conventional product showed C_{max} 37.76 μg/ml at 1.57 hr followed by a rapid fall, whereas the SR products showed slowly rising plasma levels to attain maximum concentrations (33.17, 24, and 28.54 μg/ml) at 6.29, 5, and 4 hr, respectively, followed by a more gradual fall. Peak plasma concentrations attained by products S_B and S_C are significantly lower than product S_A ($p < 0.01$). Significantly higher T_{max} values were observed with products S_A and S_B as compared to product S_C ($p < 0.05$). The extent of absorption (bioavailability) was significantly higher ($p < 0.01$) with product S_A as seen from the AUC_0^α (401.84 μg·hr/ml), followed by product S_C (324.2 μg·hr/ml), product S_B (277.38 μg·hr/ml), and CT (184.57 μg·hr/ml). The differences in C_{max}, T_{max}, and bioavailability may be due to food, gastric pH, gastric emptying time, gastric motility, rate of blood flow, and rate of metabolism (13,21,22). Absorption rate constants (K_a), absorption half-life ($T_{1/2a}$), elimination rate constant (K_e), and elimination half-life ($T_{1/2e}$) values showed a difference that was not statistically significant within the SR products. C_{max}, K_a and K_e for the CT were significantly higher than the SR products ($p < 0.001$), whereas T_{max}, $t_{1/2a}$, $t_{1/2e}$, and AUC_0^α for SR products were significantly higher than CT ($p < 0.001$).

Table 1

Pharmacokinetic Parameters of Orally Administered Conventional and Sustained-Release Marketed Ibuprofen Formulations

Products	Pharmacokinetic Parameters[a]									
	C_{max} (μg/ml)	T_{max} (hr)	$t_{1/2a}$ (hr)	$t_{1/2e}$ (hr)	K_a (hr^{-1})	K_e (hr^{-1})	AUC_0^{12} (μg·hr/ml)	AUC_0^{24} (μg·hr/ml)	AUC_0^{α} (μg·hr/ml)	% Bio-availability
CT	37.76 ± 1.60	1.57 ± 0.07	0.55 ± 0.05	3.08 ± 0.15	1.32 ± 0.09	0.23 ± 0.01	172.28 ± 10.47	NE	184.57 ± 10.12	100.00
S_A	33.17 ± 1.97	6.29 ± 0.52	2.32 ± 0.24	7.02 ± 0.62	0.32 ± 0.03	0.10 ± 0.009	235.84 ± 15.33	351.05 ± 21.92	401.84 ± 20.54	217.72[b]
S_B	24.00 ± 0.44	5.00 ± 0.49	2.08 ± 0.15	8.60 ± 0.03	0.35 ± 0.03	0.088 ± 0.007	164.24 ± 5.80	234.33 ± 9.45	277.38 ± 8.84	150.28[b]
S_C	28.54 ± 1.36	4.00 ± 0.00	2.09 ± 0.06	7.56 ± 0.73	0.33 ± 0.01	0.097 ± 0.01	191.18 ± 6.76	274.27 ± 14.67	324.21 ± 16.28	175.66[b]

NE: Not estimated.

[a]Values represent mean ± SEM (n = 7).

[b]Relative bioavailability when compared with CT.

Half Value Duration (HVD) analysis (23) was used to evaluate the sustained-release nature of the SR products. The retard quotient (R_Δ) values are summarized in Table 2. The higher R_Δ values represent greater retardation, whereas the lower values indicate lesser retardation. This confirms our results that product S_A, showing low level of drug release in vitro, showed greater retardation in vivo when compared with products S_B and S_C. The mean dissolution time (*MDT*) (24) in vivo for SR products (Table 2) showed a difference that was not statistically significant. This is in conformity with their almost identical rate and extent of dissolution. Although the mean absorption time (*MAT*) (24) for the SR products showed a difference that was not statistically significant (ANOVA), product S_B showed low *MAT* values when compared with product S_A and S_C. This difference may have influenced the C_{max}, T_{max}, and percent bioavailabilty of the products.

$MRT_{in\ vitro}$ and $MRT_{in\ vivo}$ were calculated according to Banakar (9) and Shargel (24), respectively (Table 2). $MRT_{in\ vitro}$ and $MRT_{in\ vivo}$ values showed a difference that was not statistically significant. Other variables have been derived from in vitro and in vivo data and correlated by regression analysis [Table 3 and Fig. 2(a) and 2(b)]. Since statistically significant correlations exist between the $MRT_{in\ vitro}$ and $MRT_{in\ vivo}$ or $MDT_{in\ vivo}$, the relatively simple procedure of monitoring the dissolution profile should allow the prediction of in vivo availability (25). Time to dissolve 50% and 90% are correlated better with T_{max} and C_{max}, respectively, which corresponds to the rate of absorption, and also time to dissolve 90% is better correlated with AUC_0^{12}, which reflects the extent of absorption (26).

CONCLUSION

In view of the excellent correlation observed between the in vitro and in vivo parameters in this study, the determination of $T_{50\%}$, $T_{90\%}$, and $MRT_{in\ vitro}$ would be

Table 2

Statistical Moment Parameters and Retard Quotients Calculated from Plasma Ibuprofen Profiles

Products	$MRT_{in\ vitro}$[a] (hr)	$MRT_{in\ vivo}$[b]	MDT[b]	MAT[b]	R_Δ[b]
CT	-	4.98 ± 0.13	2.35 ± 0.13	0.72 ± 0.16	-
S_A	0.581 ± 0.0027	12.57 ± 0.96	9.94 ± 0.96	2.48 ± 0.42	2.59 ± 0.44
S_B	0.576 ± 0.0028	12.83 ± 1.08	10.2 ± 1.08	1.46 ± 0.45	1.84 ± 0.31
S_C	0.562 ± 0.0028	13.48 ± 0.05	10.85 ± 0.5	2.58 ± 0.93	1.90 ± 0.27

[a]Values represent mean ± SEM (n = 3).
[b]Values represent mean ± SEM (n = 7).
$MDT_{product} = MRT_{product} - MRT_{solution}$ [$MRT_{solution}$ = 2.63 hr, Ref. 24].

Table 3

Correlation Between In Vitro Parameters and In Vivo Parameters

S No.	In Vitro Parameter	In Vivo Parameter	Correlation Coefficient	Significance Level
1	$MRT_{in\ vitro}$	$MRT_{in\ vivo}$	-0.9997	$p < 0.01$
2	$MRT_{in\ vitro}$	$MDT_{in\ vivo}$	-0.9997	$p < 0.01$
3	$MRT_{in\ vitro}$	T_{max}	0.9428	$0.05 < p < 0.1$
4	$T_{50\%}$	MAT	-0.9263	$0.05 < p < 0.1$
5	$T_{60\%}$	C_{max}	0.9199	NS
6	$T_{90\%}$	MAT	0.8641	NS
7	$T_{90\%}$	C_{max}	0.9966	$p < 0.01$
8	$T_{50\%}$	T_{max}	0.9975	$p < 0.01$
9	$T_{50\%}$	$t_{1/2a}$	0.9143	NS
10	$T_{90\%}$	AUC_0^{12}	0.9762	$p < 0.05$

NS: Not significant.

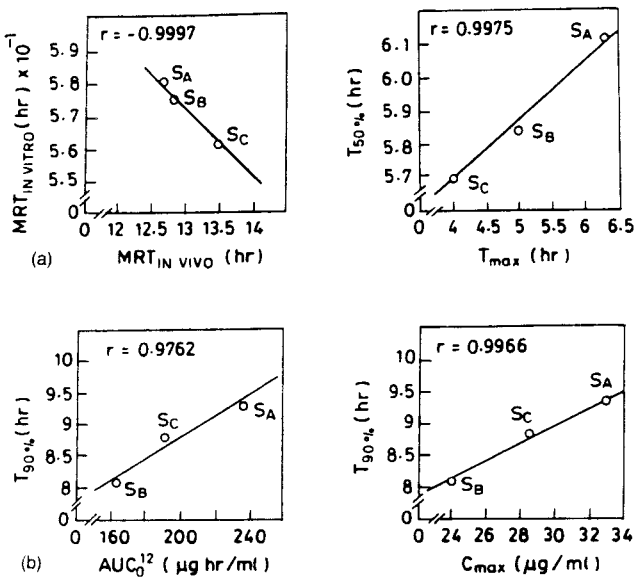

Figure 2. (a) Correlation between $MRT_{\text{in vitro}}$ and $MRT_{\text{in vivo}}$, and $T_{50\%}$ and T_{max}. (b) Correlation between $T_{90\%}$ and AUC_0^{12} or C_{max}.

useful control parameters to which each batch of the ibuprofen SR products could be submitted. Although good correlations have been obtained between the different parameters studied in this work, the usefulness of such correlations are to be checked in actual patients through pharmacodynamic studies.

ACKNOWLEDGMENT

The generous gifts of Inflakil®, Inflapen®, Ibubid®, and Ibuprofen I.P. by Targof Pure Drugs Ltd., India; Allenburys, Div. of Glaxo India Ltd; Natco Pharma Ltd., India; and Sol Pharmaceutical Ltd., India, respectively are gratefully acknowledged.

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