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Bioavailability of a controlled release indomethacin formulation in healthy subjects

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Summary

Eight healthy male subjects participated in an open-label, randomized, crossover design to determine the bioavailability of 75 mg of indomethacin in a controlled-release (cr) pellet formulation relative to an immediate-release (ir) preparation from the market. Blood samples were collected at specific times and indomethacin plasma concentrations were determined by a high-performance liquid chromatographic (HPLC) method. The maximum plasma concentration (C_{max}), the time of C_{max}(t_{max}), and the area under the plasma concentration-time curve (AUC) were calculated. Three studies were carried out. The first study (I) compared three different coating levels on the membranes of the cr pellets giving three different in vivo characteristics: slow (sp - 4 subjects), medium (mp - 8 subjects) and fast (fp - 4 subjects) release of the drug from the cr pellets, with that of ir capsules (8 subjects). The second study (II) consisted of a single-dose steady-state treatment with cr (mp) pellets, and the third study (III) compared the cr (mp) pellets, identified as the most favorable formulation from study I, with the ir indomethacin medication at steady state. The relative bioavailability (F) of the cr indomethacin formulation for a period of 24 h was 1.077.

Introduction

Indomethacin is a very effective nonsteroidal anti-inflammatory agent used in the treatment of rheumatoid arthritis. Its use is frequently limited because of significant ulcerogenic side effects (Czaky and Barnes, 1984). It seems that the high initial plasma concentration after oral administration of the drug produces adverse reactions (Alvan et al., 1975). To reduce these side effects, attempts were made to formulate indomethacin in such a way that high plasma concentrations would be prevented. Rowe and Carless (1981) observed longer, smoother plasma levels after administration of indomethacin in the form of controlled release (cr) capsules than after ingestion of conventional capsules that produce strong peaks and troughs. Several commercial cr formulations of indomethacin are on the market, but all are not of equal bioavailability (Komiyama et al., 1982). It appears that the absorption of indomethacin from the gastrointestinal tract is rapid and complete (Kwan et al., 1976), although significant variations in the peak blood levels, depending on various physiological factors have been reported (Clench et al., 1981). Aoyagi et al. (1985) have studied the effect of gastric acidity on the absorption, and thus bioavailability, of oral indomethacin. These

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authors noticed that the plasma levels of indomethacin after oral ingestion were higher in the low acidity subjects than in the high acidity subjects, indicating increased dissolution and absorption of indomethacin in a less acidic stomach.

The objective of the present study was to examine the bioavailability of a new cr formulation of indomethacin, where the release of the drug was based partly on osmosis and partly on diffusion. The development of such qualitative and reliable cr dosage form of indomethacin would decrease the frequency of administration required to maintain adequate therapeutical plasma levels and enable the maintenance of drug levels below those which produce adverse effects. The relative bioavailability of such a cr indomethacin formulation (Cr Indomethacin Pellets, Batch no. 7210, Temmler Werke, Marburg/L, F.R.G.) was determined in comparison to a conventional immediate-release (ir) capsule formulation (Indocin Capsules 25 mg — Merck, Sharpe & Dohme). In the first part of the study (I), three dosage forms with different coating levels on the membranes of the cr pellets were compared to the ir dosage form in a single dose study. In the second part of the study (II), the most favorable cr formulation from study I was administered to the subjects for eight days to determine the steady-state plasma levels of indomethacin. The third part of the study (III) compared the bioavailability of the conventional ir indomethacin formulation to that of the cr formulation at steady state.

Materials and Methods

Study design

Eight healthy male subjects between the ages of 20 and 30 years, and within ± 10% of ideal body weight, participated in the study. They were selected on the basis of their medical history, physical examination (including an electrocardiogram), clinical chemistries and hematological analyses.

The protocol for the study was approved by the Ethics Committee, Basingstoke District Hospital, U.K., and the subjects gave their informed consent.

In study I, subjects received either 25 mg of the conventional ir formulation at times 0, 6 and 12 h or capsules at time 0 h containing cr pellets, equivalent to 75 mg of indomethacin. Controlled-release formulations differed in the composition of the membrane responsible for release of the drug at various rates: slow- (sp), medium- (mp) and fast-releasing (fp) pellets (see Fig. 1 for dissolution profiles). A washout period of 14 days was allowed between each study.

During study period II the same 8 subjects received 75 mg indomethacin as cr pellets in capsules at time 0 h each day for 8 days.

In study III, the subjects were divided into two groups of four (IIIa and IIIb). One group was treated with 75 mg of cr indomethacin with optimal release rate (mp pellets) at time 0 h each day for 9 days, while the second group was treated with Indocin Capsules 25 mg at times 0, 6 and 12 h each day for 8 days and at 0 h on day 9. After a 2-week period, the order of dosing was reversed in a crossover fashion.

Study method

The subjects were asked to abstain from taking any medications for 2 weeks preceding the start of the first study and until collection of the last blood samples in the third study. Alcohol, tea, coffee and other xanthine-containing beverages were prohibited from 24 h prior to initiation of each study until its completion.

During study periods I and II each subject ingested the appropriate formulation with approx. 250 ml of water after a light breakfast. During the study period III subjects received medications after a light breakfast on days 1–8, but doses on day 9 were taken 30 min after a high-fat breakfast which consisted of the following items: bacon rashers (1 or 2), sausages (1 or 2), fried tomato portions (0 or 1), fried mushroom portions (1), fried eggs (1 or 2), fried bread slices (1/2 or 1) and decaffeinated coffee or juice. Throughout the remainder of the study periods, subjects were left on their normal daily diets.

Blood samples (10 ml) were collected from each subject prior to dosing and at the following times: after taking the ir capsules, samples were collected at 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 13, 14, 24, 26, 28,

30, 36 and 48 h (study period I), at 0 h (day 1), 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 13, 14, 15 h (day 8) and 0, 1, 2, 3, 4, 6, and 8 h (day 9) (study period III). When taking the cr capsules, samples were collected at 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 24, 26, 28, 30, 36 and 48 h (study period I). In study period II blood samples were taken at times 0 h (day 1), 0 and 3–4 h (days 3 and 4), 0 and 5–6 h (days 5, 6, and 7) and 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 24, 26, 28 and 36 h (day 8). In study period III samples were collected at 0 h (day 1), 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 15 h (day 8) and 0, 1, 2, 3, 4, 6, and 8 h (day 9).

Samples were collected in disposable plastic syringes and were immediately transferred to heparinized plastic tubes. Plasma was separated by centrifugation and was frozen at −20 °C. Plasma samples were packaged in dry ice and air-transported by UPS from U.K. to U.S.A. All samples arrived in good condition and were kept frozen (−20 °C) until the time of analysis.

A summary of the dosage forms, order of administration and number of subjects (with their initials) is presented in Table 1.

Analytical procedure

Indomethacin concentrations in plasma were determined at ambient temperature by a modification of the high-performance liquid chromatographic (HPLC) procedure reported previously (Notarianni and Collins, 1983). To 1 ml of each plasma sample in 15 ml centrifuge tubes with teflon-lined screw caps, 0.1 ml phenylbutazone (0.01 μg/ml) as an internal standard (IS) and 5 ml diethyl ether was added. The samples were mixed on a vortex mixer for 30 s followed by mechanical rotation for 10 min, and then centrifugation for 10 min at 2000 rpm. The ether layer was separated and evaporated to dryness under nitrogen gas flow at about 37 °C. The residue was reconstituted with 250 μg of mobile phase, vortexed for 30 s, and 100 μl was injected onto the column. All solvents used were of HPLC grade purity and other reagents were analytical grade.

HPLC conditions

The HPLC instrumentation consisted of a Model 6000 A solvent delivery system (Waters Associates, Milford, MA), a Model 7125 Rheodyne Injector with a 50 μl fixed loop (Rheodyne, Cotari, CA) and a Model 773 Spectroflow Variable-Wavelength UV Detector (Kratos Analytical Instruments, Ramsey, NJ). The column used was an octadecylsilane (C18) Econosphere, 5 μm, 4.5 mm i.d. × 150 mm (Alltech Associates, Deerfield, IL). The mobile phase consisted of methanol and 0.02 M potassium monobasic phosphate buffer (70 : 30) adjusted to pH 4.5 with 85% phosphoric acid. The flow rate was set at 1.5 ml/min and the peaks were monitored at a wavelength of 245 nm and 0.01 AUFS. Chromatograms were recorded and integrated using a Model C-R6A Chromatopac Integrator (Shimadzu, Kyoto, Japan).

TABLE 1

Summary of formulations, order of administration and subjects participating in the indomethacin bioavailability study

Dosage forms	Subjects in study periods				
	I		II	IIIa	IIIb
Ir capsules 25 [a]	A, B, C, D, E, H, J, K			A, B, C, D	E, H, J, K
Cr capsules 75 [b] sp		C, D, J, K			
Cr capsules 75 [b] mp	A, B, C, D E, H, J, K		A, B, C, D, E, H J, K	E, H, J, K	A, B, C, D
CR capsules 75 [b] fp		A, B, E, H			

[a] Immediate-release Indocin Capsules 25: equivalent to 25 mg indomethacin (given with 250 ml of water) at time 0, 6 and 12 h (day 1, study I) at time 0, 6 and 12 h (day 1–8) and at time 0 (day 9, study IIIa and IIIb).

[b] Controlled-release pellets 75: equivalent to 75 mg indomethacin (given with 250 ml of water) at time 0 h (day 1, study I), at time 0 h (day 1–8, study II) and at time 0 h (day 1–9, study IIIa and IIIb).

The retention times for indomethacin and the IS were 7 and 5.5 min respectively. Standard solutions of indomethacin ranging in concentration from 0.05 to 5.0 μg/ml were prepared in drug-free human plasma. 1 ml of each standard was assayed according to the procedure described above. The peak height ratio of indomethacin to IS was calculated for each chromatogram. Linear regression analysis of concentration vs peak-height ratio gave a mean slope = 0.4901, intercept = 0.0466 and mean correlation coefficient, $r = 0.999$ ($n = 6$). The calibration curve was linear over the concentration range 0.05–5.0 μg/ml. The limit of sensitivity of the assay was 0.05 μg/ml at a signal-to-noise ratio of 3 : 1. The slope and the intercept data from the regression analysis were used to solve for drug concentration in the human plasma samples. The interday relative standard deviations (RSD) of 0.1 and 2.5 μg/ml plasma samples were ±8.5 and ±5.6% ($n = 5$), respectively and the intraday RSD of 0.1 and 2.5 μg/ml were ±6.8 and ±3.4% ($n = 6$). The recovery of indomethacin and phenylbutazone at 1 μg/ml concentration was 90%.

Results and Discussion

Study I — single-dose study

The indomethacin concentration-time profiles for the ir and three cr formulations as represented by mean values are shown in Table 2. These results were used only to approximate assessment of the differences in profiles between three divided doses of ir and one single dose of cr pellets from different batches with differing dissolution profiles (Fig. 1). They were not meant for bioavailability comparison which requires evaluation at steady state.

The pharmacokinetic parameters of this study are presented in Table 3. The profiles for cr formulations (sp, mp and fp) differ from those provided by the ir formulation. The ir capsules showed t_{max} values occurring at 1–2 h after dosing, but at 5–6 h for the cr capsules. The cr formulations resulted in C_{max} values somewhat lower than those obtained with the ir capsules after dose 1 (0 h), dose 2 (6 h — except the mp formulation) and dose 3 (12 h). The ir formulation was administered at 0, 6, and 12 h; therefore there are three C_{max} values. The variation in C_{max} after the 0 h dose and the 6 and 12 h doses of the ir capsules was inconsistent. In some subjects (E, H, K) C_{max} decreased while in others (A–D, J), it fluctuated

TABLE 2

Indomethacin study I — mean concentration-time profiles for the ir and cr (sp, mp, fp) formulations (± SD values are in parentheses)

Time (h)	Indomethacin (μg/ml)			
	Ir	Cr		
		sp	mp	fp
N	8	4	8	4
0	0	0	0	0
1	0.760	0.060	0.150	0.327
	(0.68)	(0.06)	(0.13)	(0.25)
2	0.849	0.186	0.283	0.469
	(0.36)	(0.01)	(0.22)	(0.16)
3	0.566	0.278	0.417	0.676
	(0.35)	(0.06)	(0.27)	(0.32)
4	0.248	0.372	0.636	0.759
	(0.12)	(0.26)	(0.42)	(0.37)
5	0.200	0.628	0.665	0.614
	(0.10)	(0.20)	(0.41)	(0.17)
6	0.258	0.814	0.753	0.655
	(0.32)	(0.17)	(0.46)	(0.19)
7	0.833	–	–	–
	(0.33)			
8	0.696	0.418	0.306	0.392
	(0.25)	(0.28)	(0.17)	(0.13)
10	0.395	0.297	0.250	0.362
	(0.26)	(0.05)	(0.15)	(0.10)
12	0.163	0.257	0.201	0.262
	(0.09)	(0.07)	(0.13)	(0.03)
13	0.878	–	–	–
	(0.48)			
14	0.814	0.187	0.149	0.219
	(0.22)	(0.04)	(0.12)	(0.07)
24	0.425	0.146	0.158	0.196
	(0.25)	(0.06)	(0.08)	(0.08)
26	0.230	0.123	0.130	0.155
	(0.15)	(0.07)	(0.07)	(0.01)
28	0.138	0.109	0.090	0.102
	(0.10)	(0.08)	(0.07)	(0.01)
30	0.062	0.070	0.071	0.085
	(0.07)	(0.01)	(0.06)	(0.06)
36	0.030	0.045	0.055	0.047
	(0.00)	(0.03)	(0.05)	(0.03)
48	0.012	0.030	0.030	0.025
	(0.01)	(0.03)	(0.00)	(0.01)

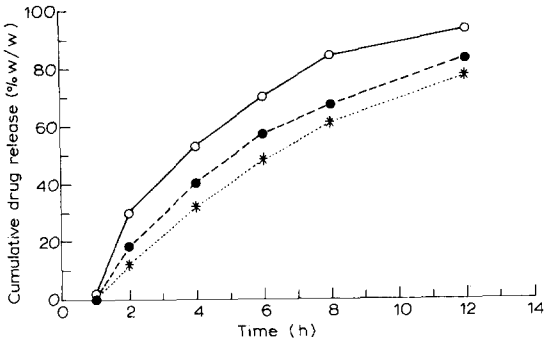

Fig. 1. Rate of indomethacin cr pellets release using a Bio-Dis dissolution apparatus and gradient pH (1 h = 4.5 pH; 2–12 h = 7.35 pH). (○———○) fp pellets; (●- - - - -●) mp pellets; (*·····*) sp pellets.

without a consistent pattern. In some subjects C_{max} was higher after the 6 h dose than after the 12 h dose and vice versa. Except for the first group of subjects (E–K), plasma levels were lower after the 6 and 12 h doses than after the 0 h dose.

All cr capsules had t_{max} values different from those for the ir capsules (Table 3), but no significant difference was detected in the t_{max} values within the cr formulations (sp, mp and fp).

The area under the plasma concentration-time curve (AUC) from time zero to the last time point (AUC_{0-t} where t is the time of the last reportable drug concentration) was determined by the trapezoidal rule (Gibaldi and Perrier, 1975).

The AUC_{0-14} values for sp and mp pellets of the cr formulation did not differ substantially, but for the fp formulation the AUC value was higher. All three formulations showed significantly lower AUC_{0-14} values than the ir formulation, except the fp pellets which had only slightly lower value. All AUC_{0-36} values for the cr capsules and the ir formulations were higher than the AUC_{0-14} values.

Study II — steady-state study (cr formulation)

In this study the cr pellets of middle release rate — mp (demonstrated to be so by in vitro dissolution study; Fig. 1) were arbitrarily chosen to determine that steady state was reached. The indomethacin mean concentration-time profiles for this cr formulation are presented in Fig. 2. From the slope of the plasma concentration-time profile on day 8 of dosing and the subsequent indomethacin concentration points, it appears that

TABLE 3

Indomethacin study I — summary of bioavailability parameters (± SD values are in parentheses)

Indomethacin parameters	IR ($N = 8$)	Cr formulation		
		Sp ($N = 4$)	Mp ($N = 8$)	Fp ($N = 4$)
C_{max} (μg/ml)	1.129 (0.41)	0.814 (0.17)	0.903 (0.45)	0.655 (0.19)
C_{max} (μg/ml)	0.873 (0.36)			
C_{max} (μg/ml)	0.999 (0.34)			
t_{max} (h)	1.50 (0.53)	6.00 (0.00)	5.63 (0.74)	5.75 (0.91)
t_{max} (h)	1.25 (0.46)			
t_{max} (h)	1.38 (0.52)			
AUC (μg h ml^{-1}) (0–14 h)	6.673 (0.50)	4.876 (0.89)	4.923 (0.82)	6.078 (0.90)
AUC (μg h ml^{-1}) (0–36 h)	12.759 (1.23)	8.100 (0.10)	7.242 (1.07)	9.771 (1.12)

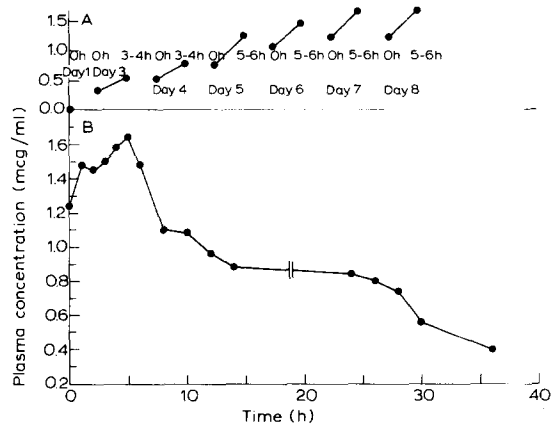

Fig. 2. Study II: plasma indomethacin concentration-time profiles for the cr (mp) formulation. The break in the curve accounts for the lack of data points between 14 and 24 h. (A) Drug concentrations at times 0 h (day 1), 0 h and 3–4 h (days 3 and 4), 0 h and 5–6 h (days 5, 6, 7, and 8). (B) Plasma indomethacin concentration-time profile at various times on day 8.

the cr capsules under investigation behave as a true cr preparation and that steady state is achieved (Fig. 2A) using this preparation on day 7. There was only a small decrease in the plasma concentration between 14 and 24 h on day 8: 0.885 and 0.840 μg/ml, respectively.

The pharmacokinetic parameters derived from these concentration-time data are summarized in Table 4. C_{max} values in this study increased from 0.9030 (study I) to 1.8456 μg/ml and t_{max} decreased from 5.63 to 3.50 h. AUC_{0-14} increased from 5.9230 (study I) to 17.7582 μg h ml^{-1} and AUC_{0-36} from 7.2424 to 33.7010 μg h ml^{-1}, showing a slow and substantial accumulation until steady-state was reached on day 7.

Study III — steady state (ir and cr formulations)

This study was designed to provide relative bioavailability data of cr pellets given once daily vs ir capsules of indomethacin at 0, 6 and 12 h at steady state.

Plasma levels of both preparations are shown in Table 5 and mean values in Fig. 3 (also separate curves are shown for subject J). The pharmacokinetic parameters of the subjects derived from these concentration-time data are summarized in Table 6 and their mean values in Table 7. The ir formulation was administered at 0, 6 and 12 h (for 8 days) and 0 h (day 9); the cr pellets were given at 0 h (for 9 days). Therefore three C_{max} and three t_{max} values for the ir formulation are presented in Table 7. Mean C_{max} and t_{max} values for both preparations are very similar: 1.66–1.80 μg/ml for the ir formulation and 1.87 μg/ml for the cr formulation. The values of t_{max} varied from 1.375 to 1.875 h for the ir capsules and it was 7.71 h for the cr pellets, which is not much different from the corresponding values obtained in study I. In study II (cr formulation only), the mean t_{max} value was less, i.e. 3.50 h.

TABLE 4

Study II: summary of indomethacin parameters' mean values on day 8 (± SD values are in parentheses)

Indomethacin parameters	Formulation: Cr Mp ($N = 8$)
C_{max} (μg/ml)	1.846 (0.658)
t_{max} (h)	3.50 (1.88)
AUC (μg h ml^{-1}) (0–14 h)	17.786 (0.51)
AUC (μg h ml^{-1}) (0–24 h)	26.325 (2.49)
AUC (μg h ml^{-1}) (0–36 h)	33.701 (3.31)

Subject J had much higher AUCs than other 7 subjects, which had similar results after three doses of ir indomethacin and after the single dose of cr pellets on day 8 (Table 6 and Fig. 3). A slower rate of elimination of the drug in J is probably responsible. In all subjects the cr pellets gave a slightly higher AUC than did the ir capsules (Table 6). Intersubject variation in AUCs for both cr pellets and ir capsules was small even though there was no control of diet, except for the light breakfast specified.

The relative bioavailability (F) of the cr indomethacin was calculated from the AUCs from study III. Table 6 contains individual areas under plasma concentration-time curves (AUCs) for 0–24 h day 8 study III of both formulations, and the individual relative bioavailabilities (F). The latter values were calculated by dividing the AUCs from the cr by the AUCs from the ir formulations.

The introduction of a high-fat breakfast at steady-state on day 9 using a single dose of both ir and cr formulations had only a minor effect (Fig. 3) on the plasma profile of subject J with high drug levels and on the other seven subjects with lower drug levels but little intersubject variation using either the ir or cr formulations, i.e. the change from a low- to a high-fat breakfast had negligible effect under steady-state conditions. Fig. 4, which provides the following mean plasma levels: day 1 (study I), day 8 (study II) and also day 8 and day 9 (study III) after the cr (mp) formulation, in conjunction with Tables 2 and 3, clearly shows the need to work at steady state when examining the relative bioavailabilities of ir and different cr formulations.

The results indicate that although a single day's dosing (as divided doses per day) of an ir formulation in comparison with single dosing of cr preparations with different dissolution profiles may

TABLE 5

Indomethacin plasma levels (μg/ml) in eight subjects after ir and cr formulations — study III/days 8 and 9 (± SD values are in parentheses)

Time (h)	Subjects								Mean
	A	B	C	D	E	H	J	K	
(ir)									
Dose 0	1.010	1.030	1.012	1.112	1.033	0.980	1.921	1.071	1.146
	(0.05)	(0.04)	(0.05)	(0.01)	(0.04)	(0.06)	(0.29)	(0.03)	(0.07)
1	1.601	1.534	1.091	1.811	1.389	1.409	2.302	1.393	1.566
	(0.01)	(0.01)	(0.18)	(0.09)	(0.07)	(0.06)	(0.28)	(0.06)	(0.09)
2	1.573	1.183	1.212	1.581	1.565	1.269	2.455	1.167	1.500
	(0.03)	(0.12)	(0.11)	(0.03)	(0.02)	(0.09)	(0.36)	(0.13)	(0.11)
3	1.174	1.080	1.211	1.422	1.157	1.167	2.179	1.113	1.312
	(0.05)	(0.09)	(0.04)	(0.04)	(0.06)	(0.06)	(0.33)	(0.08)	(0.94)
4	1.076	1.031	1.443	1.054	1.016	1.056	2.096	1.102	1.234
	(0.06)	(0.08)	(0.08)	(0.07)	(0.08)	(0.07)	(0.33)	(0.05)	(0.10)
Dose 6	1.049	0.990	1.494	1.043	0.970	1.040	2.037	1.096	1.215
	(0.06)	(0.09)	(0.11)	(0.07)	(0.09)	(0.07)	(0.31)	(0.05)	(0.11)
7	1.949	1.702	–	2.101	1.222	1.435	2.348	1.536	1.756
	(0.07)	(0.02)		(0.13)	(0.20)	(0.12)	(0.22)	(0.13)	(0.13)
8	1.568	1.476	1.375	1.760	1.581	1.273	2.663	1.255	1.619
	(0.02)	(0.05)	(0.09)	(0.05)	(0.01)	(0.13)	(0.39)	(0.10)	(0.11)
10	1.207	1.075	1.407	1.156	1.113	1.012	2.135	1.154	1.282
	(0.03)	(0.08)	(0.05)	(0.05)	(0.06)	(0.10)	(0.32)	(0.05)	(0.09)
Dose 12	1.106	0.975	1.290	1.032	1.094	0.980	2.051	1.131	1.207
	(0.04)	(0.09)	(0.03)	(0.07)	(0.04)	(0.09)	(0.32)	(0.03)	(0.09)
13	1.482	1.105	–	1.561	1.378	1.414	2.772	1.631	1.620
	(0.05)	(0.19)		(0.02)	(0.09)	(0.08)	(0.43)	(0.00)	(0.12)
14	1.831	1.894	1.100	1.318	1.187	1.141	2.640	1.511	1.578
	(0.10)	(0.12)	(0.18)	(0.10)	(0.15)	(0.17)	(0.40)	(0.03)	(0.16)
15	1.232	1.206	1.092	1.147	1.129	1.142	2.071	1.160	1.272
	(0.02)	(0.02)	(0.07)	(0.05)	(0.05)	(0.05)	(0.30)	(0.09)	(0.08)
Dose 24	1.041	1.073	1.085	1.026	0.921	0.960	2.001	1.050	1.145
	(0.04)	(0.03)	(0.02)	(0.04)	(0.08)	(0.07)	(0.32)	(0.04)	(0.08)
25	1.150	1.120	1.071	1.250	1.122	1.111	2.313	1.152	1.286
	(0.03)	(0.08)	(0.00)	(0.06)	(0.01)	(0.16)	(0.12)	(0.02)	(0.06)
26	1.614	1.260	1.231	1.720	1.403	1.381	2.242	1.604	1.551
	(0.09)	(0.09)	(0.01)	(0.32)	(0.05)	(0.08)	(0.13)	(0.12)	(0.11)
27	1.410	1.890	1.346	1.231	1.393	1.180	2.040	1.230	1.465
	(0.07)	(0.02)	(0.05)	(0.12)	(0.03)	(0.02)	(0.10)	(0.08)	(0.06)
28	1.282	1.281	1.061	1.084	1.131	1.161	2.034	1.141	1.272
	(0.11)	(0.03)	(0.13)	(0.04)	(0.08)	(0.31)	(0.01)	(0.11)	(0.10)
29	–	–	–	–	–	–	–	–	–
30	1.040	1.181	1.030	1.032	0.862	1.113	2.000	1.081	1.167
	(0.06)	(0.09)	(0.07)	(0.06)	(0.05)	(0.02)	(0.14)	(0.10)	(0.07)
32	1.020	1.063	0.960	1.000	0.841	1.020	1.884	1.040	1.104
	(0.05)	(0.07)	(0.09)	(0.06)	(0.07)	(0.05)	(0.08)	(0.05)	(0.07)
(Cr)									
Dose 0	1.021	1.072	1.189	1.132	1.087	1.051	1.990	1.021	1.195
	(0.07)	(0.05)	(0.00)	(0.02)	(0.04)	(0.06)	(0.29)	(0.07)	(0.08)
1	1.134	1.263	1.327	1.153	1.190	1.258	2.063	1.292	1.336
	(0.08)	(0.03)	(0.00)	(0.07)	(0.05)	(0.03)	(0.27)	(0.01)	(0.07)
2	1.365	1.355	1.419	1.274	1.291	1.301	2.077	1.391	1.434
	(0.03)	(0.03)	(0.01)	(0.06)	(0.05)	(0.05)	(0.24)	(0.02)	(0.06)

TABLE 5

Time (h)	Subjects								Mean
	A	B	C	D	E	H	J	K	
(Cr)									
Dose 3	1.417	1.351	1.500	1.276	1.313	1.312	2.238	1.400	1.476
	(0.02)	(0.01)	(0.01)	(0.08)	(0.06)	(0.06)	(0.28)	(0.03)	(0.07)
4	1.482	1.512	2.643	1.360	1.401	1.341	2.642	1.82	1.774
	(0.11)	(0.01)	(0.33)	(0.16)	(0.14)	(0.16)	(0.32)	(0.01)	(0.16)
6	1.600	1.644	2.312	1.591	1.443	1.416	2.895	2.021	1.865
	(0.10)	(0.08)	(0.17)	(0.10)	(0.16)	(0.17)	(0.39)	(0.06)	(0.15)
7	–	–	–	–	–	–	–	–	–
8	1.661	1.416	1.733	1.902	1.581	1.553	2.491	1.453	1.724
	(0.02)	(0.12)	(0.00)	(0.07)	(0.05)	(0.06)	(0.29)	(0.10)	(0.09)
10	1.523	1.286	1.533	1.316	1.412	1.653	2.121	1.371	1.525
	(0.00)	(0.09)	(0.00)	(0.08)	(0.04)	(0.04)	(0.22)	(0.06)	(0.06)
12	1.404	1.128	1.420	1.327	1.233	1.572	2.100	1.102	1.411
	(0.00)	(0.11)	(0.00)	(0.03)	(0.07)	(0.06)	(0.26)	(0.12)	(0.08)
13	–	–	–	–	–	–	–	–	–
14	1.369	1.123	1.323	1.318	1.134	1.329	2.043	1.089	1.341
	(0.01)	(0.08)	(0.01)	(0.01)	(0.08)	(0.01)	(0.27)	(0.09)	(0.07)
15	1.263	1.120	1.300	1.290	1.135	1.246	2.001	1.078	1.304
	(0.02)	(0.07)	(0.00)	(0.00)	(0.06)	(0.02)	(0.26)	(0.08)	(0.06)
Dose 24	1.065	1.031	1.167	1.031	1.031	1.027	2.002	1.056	1.176
	(0.04)	(0.06)	(0.00)	(0.05)	(0.05)	(0.06)	(0.31)	(0.04)	(0.07)
25	1.021	1.150	1.234	1.232	1.183	1.150	2.140	1.182	1.286
	(0.01)	(0.12)	(0.01)	(0.00)	(0.05)	(0.05)	(0.02)	(0.30)	(0.07)
26	1.213	1.264	1.362	1.246	1.203	1.241	2.261	1.220	1.420
	(0.00)	(0.03)	(0.07)	(0.06)	(0.06)	(0.00)	(0.01)	(0.05)	(0.04)
27	1.296	1.392	1.458	1.302	1.240	1.352	2.394	1.362	1.475
	(0.11)	(0.02)	(0.12)	(0.01)	(0.08)	(0.12)	(0.05)	(0.02)	(0.07)
28	1.404	1.565	1.713	1.546	1.264	1.492	2.912	1.380	1.660
	(0.13)	(0.12)	(0.07)	(0.10)	(0.02)	(0.03)	(0.11)	(0.01)	(0.07)
29	1.542	1.770	1.692	1.565	1.285	1.554	2.721	1.492	1.703
	(0.09)	(0.09)	(0.01)	(0.12)	(0.00)	(0.01)	(0.07)	(0.06)	(0.06)
30	1.610	1.735	1.591	1.790	1.431	1.690	2.729	1.562	1.767
	(0.06)	(0.01)	(0.08)	(0.01)	(0.02)	(0.08)	(0.02)	(0.04)	(0.04)
32	1.500	1.652	1.431	1.653	1.352	1.353	2.621	1.512	1.634
	(0.12)	(0.20)	(0.09)	(0.09)	(0.01)	(0.03)	(0.10)	(0.01)	(0.09)
36	1.071	1.134	0.996	1.178	1.091	1.111	2.040	0.922	1.193
	(0.01)	(0.07)	(0.11)	(0.01)	(0.03)	(0.01)	(0.03)	(0.11)	(0.05)

be used to assess broadly the different rates of release in vivo, it is essential to work at steady state to compare relative bioavailabilities of ir vs cr preparations of indomethacin. Using the chosen cr preparation, 7–8 days dosing were required to achieve steady-state conditions. The steady state in vivo study (involving comparison of a batch of cr and ir preparations) shows that the cr pellets have a rate of release in vivo which, upon once per day dosing, can be used to produce a steady plasma profile without loss of bioavailability to replace a daily intake of ir formulation given in divided doses at 0, 6 and 12 h. The differences between plasma plateaus and troughs of cr drug are slightly less than the divided doses of the ir formulation.

Although one of the eight subjects differed greatly, with respect to plasma levels, from the other seven, the crossover comparison between the ir and cr formulations gave results comparable to those obtained from the other seven. This indicates that changing the dosage regimen from three

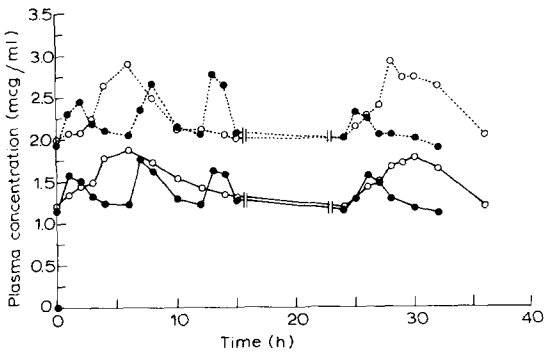

Fig. 3. Study III: plasma indomethacin concentration-time profiles for the ir and cr formulations; days 8 and 9. (○———○) cr formulation; (●———●) ir formulation; (○·····○) subject J cr formulation; (●·····●) ir formulation.

doses of the ir preparations to a daily dose of the cr preparation will not be dependent on intersubject variations in the rate of elimination of the drug under steady-state conditions upon taking cr product.

TABLE 6

Study III — individual areas under the curve (AUC_{0-24}) and relative bioavailabilities (F), day 8 (± SD values are in parentheses)

Subjects	AUC_{0-24} (μg h ml^{-1})		F
	ir	cr	
A	30.480	32.100	1.661
	(0.34)	(0.64)	(0.22)
B	28.640	29.590	1.033
	(1.04)	(1.59)	(0.02)
C	29.209	34.534	1.182
	(0.82)	(2.77)	(0.04)
D	30.245	31.585	1.044
	(0.43)	(0.84)	(0.01)
E	27.260	29.730	1.091
	(1.56)	(1.54)	(0.01)
H	26.840	31.485	1.173
	(1.72)	(0.54)	(0.04)
J	49.895	50.505	1.012
	(7.00)	(6.31)	(0.02)
K	28.545	30.880	1.082
	(1.08)	(1.10)	(0.00)
Mean	31.390	33.801	1.077
	(1.74)	(1.92)	(0.05)

TABLE 7

Study III — summary of indomethacin bioavailability parameters, day 8 (± SD values are given in parentheses)

Parameter	Formulation		F
	Ir ($N = 8$)	Cr ($N = 8$)	
C_{max} (μg/ml)	1.658	1.873	
	(0.09)	(0.14)	
C_{max} (μg/ml)	1.800		
	(0.13)		
C_{max} (μg/ml)	1.700		
	(0.13)		
t_{max} (h)	1.875	7.710	
	(0.41)	(0.40)	
t_{max} (h)	1.625		
	(0.30)		
t_{max} (h)	1.375		
	(0.18)		
AUC (μg h ml^{-1})	20.060	20.600	1.027
(0–14 h)	(1.30)	(0.91)	(0.04)
AUC (μg h ml^{-1})	31.389	33.801	1.077
(0–24 h)	(1.75)	(1.92)	(0.04)

A change from a light breakfast to a high-fat breakfast at steady state did not change the drug plasma profile for the cr product even if the subjects differed in their rate of elimination and thus their plasma levels of the drug, i.e. 'dose dumping' from the cr product did not occur after a high-fat meal.

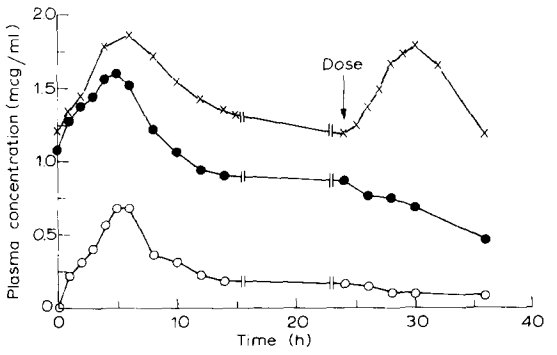

Fig. 4. Plasma indomethacin concentration-time profiles for the cr formulation, based on mean data. The results are summarized on day 1 (○) of study I, day 8 (●) of study II and days 8 and 9 (*) of study III. Additional dose of 75 mg is administered at time 0 h, day 9 of study III.

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