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Pharmacokinetic evaluation of osmotically controlled indomethacin delivery systems in man

J.D. Rogers *, R.B. Lee *, P.R. Souder *, R.K. Ferguson ***, R.O. Davies *, F. Theeuwes ** and K.C. Kwan *

* *Merck Sharp and Dohme Research Laboratories, West Point, PA;* ** *ALZA Research, Palo Alto, CA; and* *** *Thomas Jefferson University, Philadelphia, PA (U.S.A.)*

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Summary

Absorption characteristics of two osmotic delivery systems for indomethacin have been evaluated in man following single-dose administration as compared to intravenous and capsule administration of the drug. Fifteen healthy volunteers received all treatments according to a latin square design. Initial appearance rates of indomethacin in the general circulation following oral administration of the osmotically controlled delivery systems mimic their constant delivery rates found in vitro. The renal clearance and urinary recovery of free plus conjugated indomethacin is comparable in all treatments. Compared to intravenous or capsule administration of indomethacin, drug is 84% bioavailable from either controlled-release preparation.

Introduction

Gastrointestinal therapeutic systems (GITS) function according to the principles of an elementary osmotic pump whereby drug delivery is affected through osmotic control (Theeuwes, 1975). GITS consists of an osmotic core, containing drug and excipients, and is coated with a semipermeable membrane (Fig. 1). Upon exposure to an aqueous environment, the core imbibes water at a controlled rate that is governed by membrane permeability to water and the solubility of the core formulation. This activity creates an osmotic pressure gradient across the semi-permeable membrane. Pressure may be relieved only by extrusion of a saturated solution of drug and excipient through a small delivery orifice which is engineered into the membrane to minimize the effects of diffusive and convective flow. Hence, while

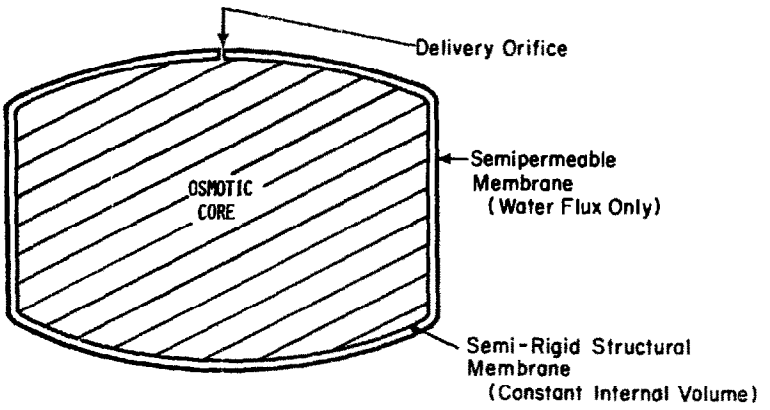

Fig. 1. Schematic representation of gastrointestinal therapeutic systems (GITS).

undissolved drug remains, the internal drug solution is saturated and delivery through the orifice is zero-order. Eventually, continued water influx depletes the solid drug core, dilutes the internal drug solution, and causes the delivery rate to decline continuously towards zero. The unit stops functioning when the osmotic pressure gradient vanishes. Hence, as only water is imbibed, the rate of drug delivery from GITS is independent of pH and agitation, but dependent on membrane permeability and the combined solubility of drug and excipients (Theeuwes et al., 1983).

Other reports from these laboratories have discussed the design of GITS-indomethacin including their evaluation in vitro, in the dog, and after repeated administration in man (Theeuwes et al., 1983; Bayne et al., 1982). This report compares absorption and disposition characteristics of indomethacin in man following single doses of two different GITS (A and B), following capsule administration, and following intravenous administration of the drug.

Materials and Methods

Dosage forms

GITS-A and GITS-B are designed to deliver 75 mg of drug in approximately 11 and 8 h, respectively. Each GITS contains a calculated excess to allow for drug remaining inside the module when iso-osmotic conditions prevail. The nominal dose of 75 mg was used in all estimates of bioavailability. Indomethacin capsules (INDOCIN 25 mg) and an intravenous preparation of indomethacin were also used in this study.

Study design. Fifteen healthy male volunteers participated in a single-dose, 5-way cross-over study. Each subject received the 5 treatments listed below at weekly intervals according to a latin square design.

Treatment A: GITS-A
Treatment B: GITS-B
Treatment C: Indomethacin capsules, 3 × 25 mg

Treatment D: Indomethacin capsules, 25 mg at 0, 4, and 8 h (3 doses)
Treatment E: Bolus i.v. injection of indomethacin; 20 mg

During all oral treatments blood samples were obtained at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 12 h. For the intravenous treatment blood was sampled through 8 h, but more frequently during the first 90 min. Total urine was collected for 72 h during each treatment period, with increments of 1 or 2 h duration being collected for the first 12 h.

Drug analysis

Plasma and syringe/vial samples were analyzed for free indomethacin by a gas chromatographic technique using electron capture detection (Ferry et al., 1974; Helleberg, 1976). Urine specimens were analyzed for total indomethacin by the same technique following enzymatic hydrolysis of the samples. The method is specific for indomethacin.

Data analysis

The biotransformation of indomethacin in man has been shown to be independent of the route of drug administration (Kwan et al., 1976). Hence, following oral, rectal or intravenous administration, indomethacin undergoes demethylation and deacylation to form O-desmethylindomethacin, N-deschlorobenzoylindomethacin, and O-desmethyl-N-deschlorobenzoylindomethacin. In urine, unchanged drug and metabolites are present both as they are and as their glucuronide conjugates (Duggan et al., 1972). In plasma and feces only the unconjugated forms are found. Studies have shown indomethacin to be 100% and 80% bioavailable following oral and rectal drug administration, respectively, as compared to an intravenous dose (Kwan et al., 1976).

Indomethacin also undergoes appreciable enterohepatic circulation in man (Duggan et al., 1975). Since indomethacin is quantitatively absorbed from the GI tract, the amount of indomethacin appearing to enter the general circulation following any route of administration may exceed the administered dose. This process is unpredictable because of the periodic, but irregular, nature of gall bladder emptying. Kwan et al. (1976) have demonstrated, however, that a two-compartment, open-model adequately described indomethacin disposition in man if one accounts for the biliary recycling of the drug as an additional input of drug into the general circulation.

Plasma data collected during the intravenous portion in this study were treated in this manner to determine the individual pharmacokinetic parameters for indomethacin. The individual plasma clearance ($\dot{V}_{Cl,P}$) of indomethacin in this treatment was obtained from the volume of distribution of drug in the central compartment (V_1) and the elimination rate constant (k_{10}) as shown in Eqn. 1.

$$\dot{V}_{Cl,P} = V_1 k_{10} \tag{1}$$

Estimates of area under the individual plasma concentration–time profiles (AUC) in all treatments were obtained by the trapezoidal method.

Since conjugated indomethacin is not present in plasma, the renal clearance

($\dot{V}_{Cl,R}$) of the drug is operationally defined (Kwan et al., 1976) as the ratio of free plus conjugated indomethacin in urine (U_{0-t}) to the AUC for indomethacin (see Eqn. 2).

$$\dot{V}_{Cl,R} = \frac{U_{0-t}}{(AUC)_0^t} \tag{2}$$

In essence, the renal clearance of indomethacin is indicative of indomethacin elimination by renal excretion and glucuronidation permitting a broader perspective of the overall elimination of the drug. Since the enterohepatic circulation of indomethacin precludes the extrapolation of AUC by conventional techniques, $[AUC]_0^\infty$ obtains by rearrangement of Eqn. 2.

$$[AUC]_0^\infty = \frac{U_{0-\infty}}{\dot{V}_{Cl,R}} \tag{3}$$

Individual non-renal clearance ($\dot{V}_{Cl,NR}$) as determined from the intravenous portion of the study ($\dot{V}_{Cl,NR} = \dot{V}_{Cl,P} - V_{Cl,R}$) was assumed to remain constant in all other treatments. Hence, individual plasma clearance in all oral treatments ($\dot{V}^*_{Cl,P}$) derives from treatment specific estimates of renal clearance and $\dot{V}_{Cl,NR}$.

The fraction of the indomethacin dose which is available to the general circulation following intravenous administration ($F_{i.v.}$) is estimated by Eqn. 4

$$F_{i.v.} = \frac{[AUC_{i.v.}]_0^\infty \cdot \dot{V}_{Cl,P}}{Dose_{i.v.}} \tag{4}$$

F values for orally administered indomethacin can be derived from treatment specific estimates of $[AUC]_0^\infty$, $\dot{V}^*_{Cl,P}$ and dose. The bioavailability of that treatment relative to intravenous drug administration is then (Kwan and Till, 1973):

$$\text{Bioavailability} = F/F_{i.v.} \tag{5}$$

Absorption profiles and estimates of the amount of drug in the body were made using the method of Loo and Riegelman (1968) which was modified to use spline interpolation (Yeh and Kwan, 1978). These procedures do not distinguish drug absorbed for the first time from that being reabsorbed. The total amount of drug absorbed and reabsorbed represents the product of the treatment specific F and the dose of indomethacin administered.

Statistically, posterior probabilities were calculated for all bioavailability ratios (Rodda and Davis, 1980).

Results

During the drug analysis portion of this study, plasma volumes analyzed ranged from 0.05 ml to 0.50 ml. The daily standard curve was linear from 1.0 to 500 ng per

TABLE 1

MEAN PHARMACOKINETIC PARAMETERS FOR INDOMETHACIN FOLLOWING INTRAVENOUS ADMINISTRATION (n = 14)

Parameter	Value
k_{12} (h^{-1})	1.12 (0.57) [a]
k_{21} (h^{-1})	2.91 (1.06)
k_{10} (h^{-1})	1.48 (0.25)
V_1 (liters)	5.1 (0.9)
$f_{i.v.}$	0.27 (0.05)
$\dot{V}_{Cl,R}$ (ml/min)	25.8 (6.7)
$\dot{V}_{Cl,P}$ (ml/min)	123.9 (26.9)
$\dot{V}_{Cl,NR}$ (ml/min)	98.2 (21.4)
$F_{i.v.}$	1.3 (0.2)

[a] Standard deviation in parentheses following value.

0.10 ml control plasma. Sample concentrations below the lower limit of the curve were reported as zero.

The coefficients of variation (C.V.) for replicate (n = 10) standards of 25.0, 50.0 and 250 ng in control plasma were 4.7%, 5.8% and 3.2%, respectively.

Urine volumes assayed ranged from 0.05 to 0.50 ml. The daily standard curve was linear from 10.0 to 400 ng per 0.10 ml control urine. Samples whose concentrations exceeded the upper limit of the standard curve were diluted and reassayed. Those falling below the lower limit were reported as zero.

The C.V.s for replicate (n = 8) standards of 25.0, 100 and 300 ng in urine were 3.7%, 3.0% and 1.1%, respectively.

Table 1 presents mean results from the i.v. portion of the study. The fraction of the dose ($f_{i.v.}$) recovered in urine (free plus conjugated indomethacin) was 0.27. The renal clearance was 25.8 ml/min while approximately 30% of the intravenous dose

TABLE 2

MEAN PLASMA LEVEL AND URINARY EXCRETION PARAMETERS (±S.D.) FOLLOWING A SINGLE-DOSE OF GITS-A, GITS-B, INDOMETHACIN CAPSULES 75 mg (3×25 mg), OR INDOMETHACIN 25 mg CAPSULES GIVEN AT 0, 4 AND 8 h

Parameter	GITS-A	GITS-B	Indomethacin Caps. 3×25 mg	Indomethacin Caps 25 mg t.i.d.
Urinary recovery (mg)	16.6 (±4.5)	16.3 (±4.0)	17.9 (±3.1)	18.7 [a] (±3.4)
$\dot{V}_{Cl,R}$ (ml/min)	23.3 (±5.0)	23.6 (±5.6)	23.2 (±5.3)	23.5 (±5.2)
$\bar{C}p_{12}$ (μg/ml)	0.68 (±0.18)	0.76 (±0.18)	1.00 (±0.33)	0.67 (±0.20)
Mean bioavailability (vs i.v.)	0.85 [a]	0.84 [a]	1.04 [a]	1.03 [b]
$[AUC]_0^\infty$ (μg·h/ml)	12.27 (±3.91)	11.86 (±3.39)	13.50 (±3.88)	13.50 [a] (±3.53)

[a] n = 14.
[b] n = 13.

was recycled via the bile. That is to say, the fraction of an i.v. dose ($F_{i.v.}$) available to the general circulation is 1.3.

Table 2 summarizes mean results obtained following all oral treatments in the study. Mean urinary recovery of free plus conjugated indomethacin following a single dose of GITS-A or GITS-B was approximately 16 mg each. This compares to a recovery of 18–19 mg following either indomethacin capsule regimen. Mean renal clearance following all treatments was nearly 23 ml/min.

The mean 12-h plasma concentration ($\bar{C}p_{12}$) for the GITS-A, and indomethacin 25 mg capsules given t.i.d. was 0.68 and 0.67 μg/ml, respectively. The other two regimens registered somewhat higher $\bar{C}p_{12}$, namely, 0.76 μg/ml for GITS-B and 1.0 μg/ml for indomethacin capsules 75 mg (3 × 25 mg). The similarity of these results was corroborated by bioavailability estimates which showed GITS-A and GITS-B to be 85% and 84% bioavailable, respectively, as compared to intravenous administration of the drug. Indomethacin was 100% bioavailable from capsule regimens. The posterior probability was greater than 95% that the true difference in bioavailability among all treatments is less than 25% (Table 3).

Mean indomethacin plasma concentration profiles are shown in Figs. 2 and 3. Plasma profiles following GITS administration rise and fall more slowly while GITS-A exhibits lower maximum plasma concentrations than those following capsule administration. Interestingly, the mean plasma profile for the 4-hourly 25 mg capsule regimen does not show a peak following the second dose. Individual plasma profiles showed this peak, but it occurred at various times between the second and third dose of indomethacin. Since study participants fasted prior to each treatment period and were allowed to eat 3 and 6 h thereafter, delays in drug absorption are not unexpected. However, this did not alter the extent of drug absorption.

Fig. 4 displays mean cumulative indomethacin absorption profiles for all oral treatments. Among treatments, the total amount of drug absorbed and reabsorbed is within 20% of each other. The initial rate of drug absorption following GITS administration is slower than that following either capsule regimen. More importantly, however, the initial rates of drug absorption are different for GITS-A and GITS-B, and they are constant for at least 4 h. The absorption rates in vivo are practically identical to in vitro drug release rates, i.e. 7.8 mg/h for GITS-A and 9.4

TABLE 3

POSTERIOR PROBABILITIES FOR BIOAVAILABILITY RATIOS

Bioavailability	Probably that % difference is less than:			
	15	20	25	30
GITS-A vs i.v.	0.494	0.837	0.973	0.997
GITS-A vs 25 mg cap.	0.490	0.800	0.954	0.993
GITS-B vs i.v.	0.439	0.825	0.975	0.997
GITS-B vs 25 mg cap.	0.299	0.808	0.985	0.999
3 × 25 mg cap vs i.v.	0.964	0.994	0.999	> 0.999
25 mg cap vs i.v.	0.974	0.996	0.999	> 0.999

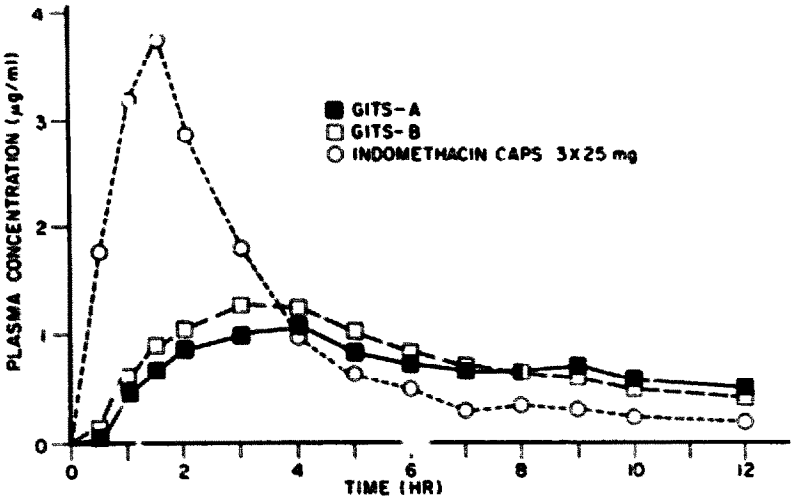

Fig. 2. Mean plasma concentrations of indomethacin.

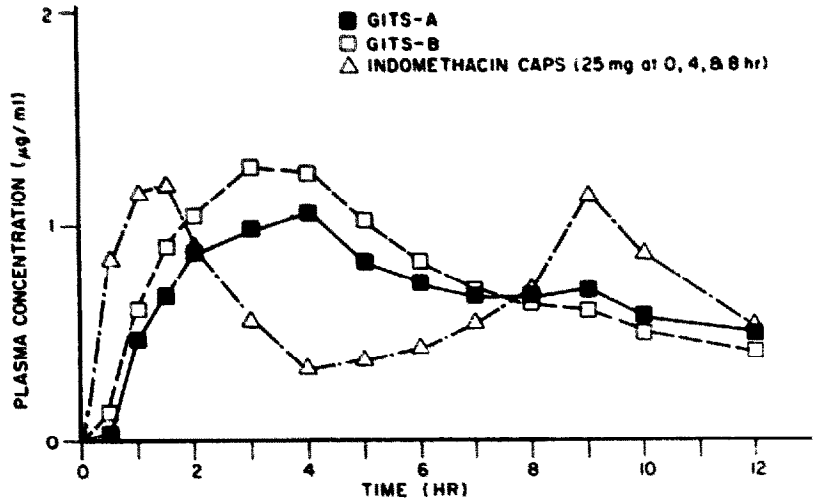

Fig. 3. Mean plasma concentration of indomethacin.

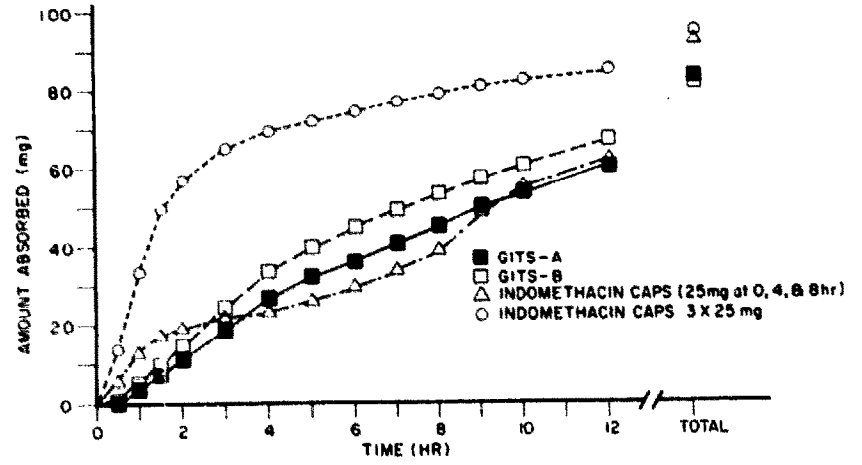

Fig. 4. Mean cumulative amount of indomethacin absorbed from the gastrointestinal tract.

TABLE 4

ESTIMATES OF INDIVIDUAL INDOMETHACIN ABSORPTION RATES FROM THE GASTRO-INTESTINAL TRACT FOR THE FIRST 4 h FOLLOWING ORAL ADMINISTRATION OF GITS-A OR GITS-B

Subject no.	Absorption rates (mg/h)	
	GITS-A	GITS-B
1	7.83	10.05
2	5.84	9.82
3	6.43	10.07
4	8.16	8.88
5	6.79	9.53
6	11.11	10.76
7	8.76	6.25
8	8.10	10.14
9	6.46	9.61
10	7.10	11.44
11	9.03	8.88
12	7.85	8.64
13 [a]	–	–
14	6.73	7.73
15	8.61	10.04
Mean (±S.D.)	7.77 [b] (±1.37)	9.42 (±1.30)

[a] Did not receive intravenous portion of study per protocol.
[b] Significantly less than GITS-B, $P < 0.01$.

mg/h for GITS-B (Table 4) compared to in vitro release rates of 7 and 9 mg/h (Theeuwes et al., 1983), respectively. Furthermore, the observed in vivo rates are significantly different.

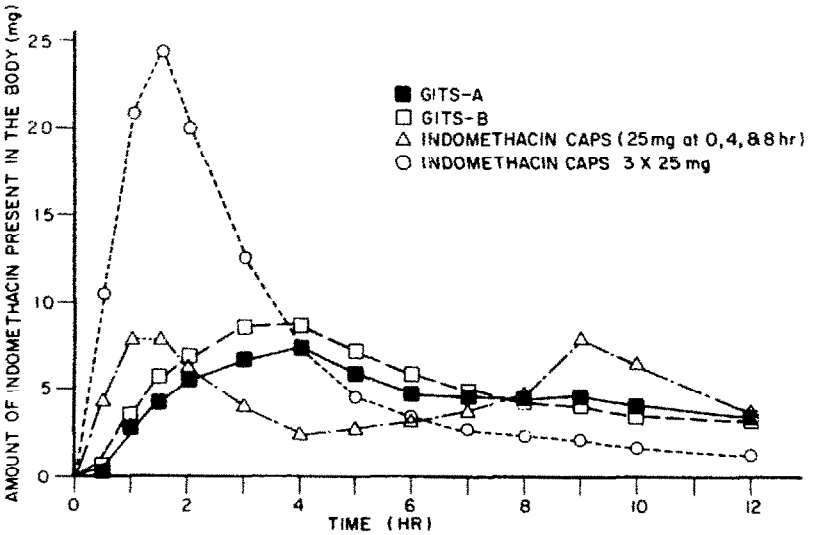

Fig. 5. Mean body levels of indomethacin.

Finally, mean body drug level profiles following all regimens are shown in Fig. 5. These profiles illustrate that indomethacin levels in the body tend to be more uniform and sustained over time following GITS administration.

Discussion

Maintenance of minimally effective levels of drug in blood has long been sought as a rational approach to drug therapy in man. Seldom does drug delivery via conventional dosage forms approach this goal. So-called sustained-, delayed-, or controlled-release dosage forms generally offer only an approximate first-order presentation of drug to the system. The advent of gastrointestinal therapeutic systems with their inherent zero-order delivery rates brings constant and maintained blood levels of drug within the reach of the pharmaceutical chemist and the prescribing physician. The pharmacokinetics of indomethacin in man has been well studied. The apparent half-life of drug in plasma is 4 h and absorption following oral administration is efficient and complete. These attributes, coupled with its 3–4-times daily dosage schedule, make indomethacin an ideal candidate for this type of controlled drug delivery. Similar systems, in one form or another, have been used experimentally in animals for years (Pinedo et al., 1976; Arimura et al., 1977; Siew and Goldstein, 1978; Sikic et al., 1978; Frankel et al., 1979; Pratt et al., 1979; Ellison et al., 1980; Nau et al., 1981). Their successful evolution into oral dosage forms for human use is self-evident by the results described herein for GITS-indomethacin.

Two osmotically driven GITS-indomethacin dosage forms were evaluated pharmacokinetically in man via a single-dose cross-over study. Comparative standards were i.v. indomethacin as well as two indomethacin capsule regimens, i.e. 3×25 mg and 25 mg every 4 h for 3 doses. The two GITS formulations were designed to deliver indomethacin in approximately zero-order fashion with 75 mg of drug being released in approximately 11 (GITS-A) or 8 h (GITS-B).

Nearly comparable amounts of indomethacin are available to the general circulation from GITS-A or GITS-B and from indomethacin capsules. Also, plasma level information indicates that one GITS-A most closely emulates a 25-mg indomethacin capsule regimen given every 4 h. Because of enterohepatic circulation, constant plasma levels of indomethacin should not be expected even if drug delivery were perfectly zero-order. Nevertheless, rates of drug delivery to the general circulation appear constant for about 4 h after GITS administration and the slopes match those found in vitro. Even though the delivery rates for the two GITS differ by less than 20%, they are clearly distinguishable from each other in vivo.

Previous studies in the dog indicated that the release rate of GITS-indomethacin in the gastrointestinal tract are identical to those in vitro (Theeuwes et al., 1983). In this present study, attenuations in the rate of delivery 4 h following the administration of either GITS suggest that the drug absorption is less efficient at subsequent times. Absorption of indomethacin may be inherently less efficient from the distal portions of the gastrointestinal tract, or drug diffusion from the exit ports to the

mucosal surface may be increasingly hindered. In either event, the net effect is that the bioavailability of indomethacin from GITS is about 85% compared to 100% for capsules.

Hence, the transition from theory to animals to man has been accomplished for controlled drug delivery systems that are driven by an osmotic pressure gradient for a predetermined length of time. Indomethacin is delivered by GITS in amounts equivalent to typical capsule regimens, but in a fashion which avoids the plasma level excesses and shortages noted with conventional dosage forms. Future reports will pertain to the performance of these systems in clinical trials of efficacy and patient acceptance.

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