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# OROS® OSMOTIC SYSTEM DEVELOPMENT

Felix Theeuwes, D.Sc.
ALZA Corporation
950 Page Mill Road
Palo Alto, CA 94304

## INTRODUCTION

Pharmacologists now recognize that many drugs for chronic administration should be dosed on a schedule that maintains the plasma concentration within a safe and effective range. Conventional dosage forms often produce plasma fluctuations that exceed the maximum safe therapeutic level and decline below the minimum effective level (Figure 1); the ratio of these two levels is known as the therapeutic index (TI). Conventionally, the aim has been to minimimze fluctuations by dosing at frequent time intervals ($\tau$), as shown in Figure 1. Using equation 1, one can determine for conventional dosage forms the dosing interval that will maintain plasma concentration within the therapeutic concentration range.

$$\tau \leq t_{1/2} \frac{\ln TI}{\ln 2} \qquad \text{Eq. 1}$$

The constraints imposed by equation 1, however, very often produce dosage forms with inconveniently frequent dosing intervals that are shorter than the already short half-lives (e.g., 2-4 hours) of the drugs.

Research in controlled-release dosage forms aims at designing a system with a zero-order input Z



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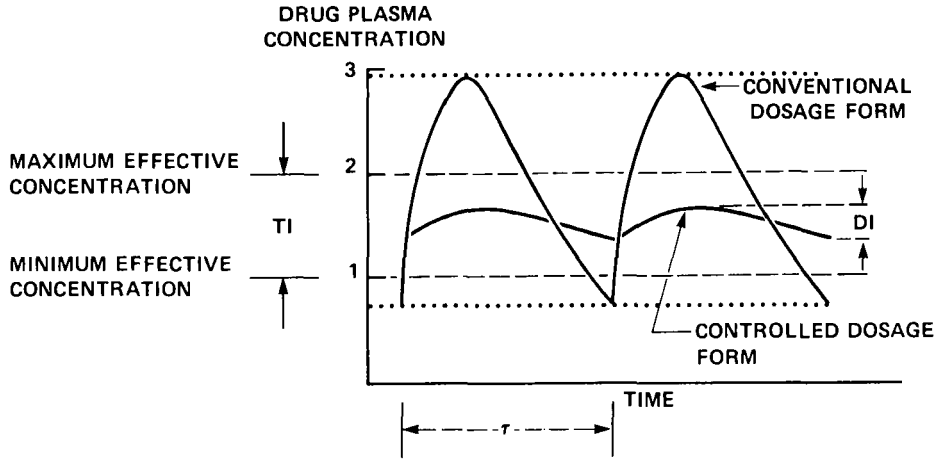


FIGURE 1
Schematic representation of drug plasma concentration profiles at steady state following administration of a conventional bolus dosage form and a controlled-release dosage form. (From: F. Theeuwes & W. Bayne, in "Controlled Release Pharmaceuticals," J. Urquhart, ed., APhA, Washington, D.C., p. 61, 1981).

(i.e., zero-order delivery rate from the dosage form) that produces the optimal plasma concentration ($C_p$) given by equation 2:

$$Z = C_p \cdot \dot{V}_{cl} \qquad \text{Eq. 2}$$

where $\dot{V}_{cl}$ is drug clearance.

Figure 2 illustrates an *in vitro* zero-order delivery rate that is equal to the rate *in vivo* into the gastrointestinal tract from a controlled-release system and the subsequent plasma concentrations. The plasma concentration profile reflects the delivery profile into the gut, although oscillations appear somewhat dampened. Plasma fluctuations with such a system can be expressed by the dosage form index (DI)[1], the ratio of the maximum-to-minimum plasma concentration achieved within a dosing interval. Dosage forms producing controlled therapy will have

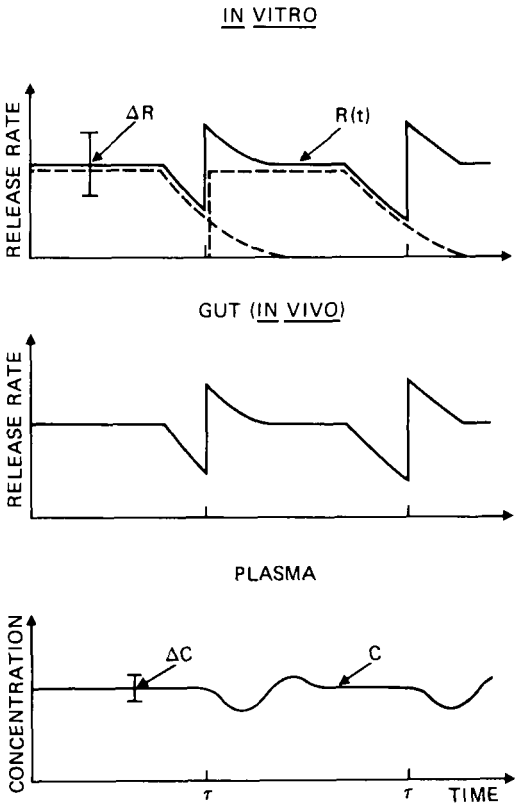


FIGURE 2
Stylized representation of in vitro release rate, resultant total release rate, and desired plasma concentrations. (From: F. Theeuwes & W. Bayne, in "Controlled Release Pharmaceuticals", J. Urquhart, ed., APhA, Washington, D.C., p. 61, 1981).

a dosage form index smaller than the therapeutic index of the drug.

In this paper, I will address the key events that form the basis of rational dosage form design and the testing plan to achieve an optimal dosage form and dosage regimen. For illustrative purposes, I will discuss the development of the elementary osmotic pump for indomethacin (EOP-indomethacin).

## ELEMENTARY OSMOTIC PUMP AS AN ORAL DOSAGE FORM

The elementary osmotic pump[2] (EOP, Figure 3) is a new dosage form for dispensing drugs to the gastrointestinal tract, one that delivers drug at a rate independent of gastrointestinal tract pH and motility. The EOP comprises a solid core, semipermeable membrane coating, and laser-drilled delivery orifice. This pump utilizes osmosis as its driving force: water imbibed from the environment crosses the membrane at a controlled rate and causes the drug solution to exit through the delivery orifice. Delivery rate is controlled by osmotic properties of the core and membrane area, thickness, and permeability to water. Figure 4 shows an actual system in operation. The system--laying on a ledge in a vial--is submersed in water with the orifice pointing downward. The system imbibes water and dispenses drug contained within the system (dye was used for illustrative purposes here). The constant stream of drug from the system indicates constancy of release rate. If we measure the amount of drug leaving the orifice per unit time, the delivery rate profile obtained would closely resemble the release rate profile shown in Figure 5[2]. The release rate curve is constant up to time $t_z$ at which time the last of the solid dissolves within the membrane shell. At that point the osmotic pressure declines leading to a decrease in imbibition rate and drug concentration and hence a decline in release rate. This figure also shows the correlation between the actual range of 5 experimental potassium chloride systems and the calculated rate.

Before starting to design the elementary osmotic pump, we considered the most desirable functional lifetime for the system. A study by Hinton[3] indicated that an inert object has an average transit time

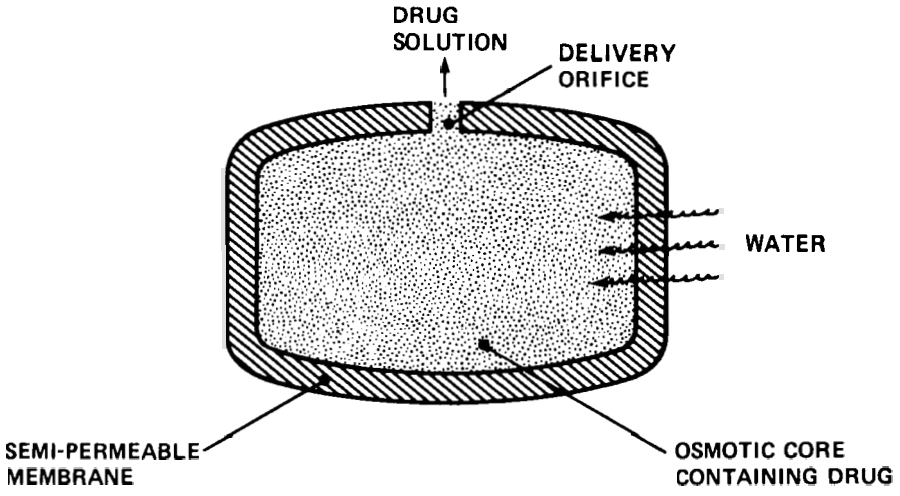


FIGURE 3
Cross-section of the elementary osmotic pump[2].

from mouth to anus of about 25-30 hours (Figure 6). These data suggest that the duration of delivery time from a single system must be shorter than 24 hours in order to allow absorption of a significant portion of drug. Dosing time, however, may be selected to be longer than the delivery time and should be convenient for the patient (for instance, dosing every 12 or 24 hours).

Dosage form design is aimed at controlling the plasma concentration or pharmacological effect with a minimum dosage of drug and a convenient dosing frequency. This dosing interval comprises two components--absorption time (loading phase) and discharge time. Discharge time is the pharmacokinetic or pharmacodynamic excretion phase. Absorption time equals the system's delivery time when the dosage form is rate controlling. The latter is designed to give an acceptable extent of absorption for maximum plasma concentration or effect control and to be commensurate with a convenient dosing interval.

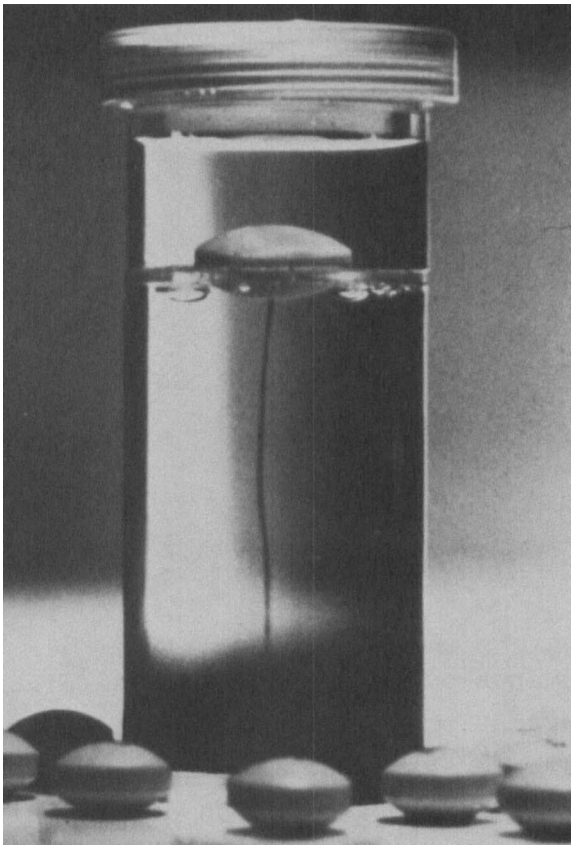

FIGURE 4
The elementary osmotic pump in operation. The system rests on a ledge in the vial; dye (simulating active agent) is pumped from the delivery orifice. (From: F. Theeuwes & B. Eckenhoff, in "Controlled Release of Bioactive Materials," R. Baker, ed., Academic Press, NY, p. 61, 1980).

## DEVELOPMENT OF THE EOP-INDOMETHACIN[4]

We aimed to design a controlled release rate dosage form for indomethacin that would control the quality of treatment, that is, one that would deliver drug independent of its environment. Subsequent stages of research in the gastrointestinal tract verified the *in vitro* constancy of the release rate.

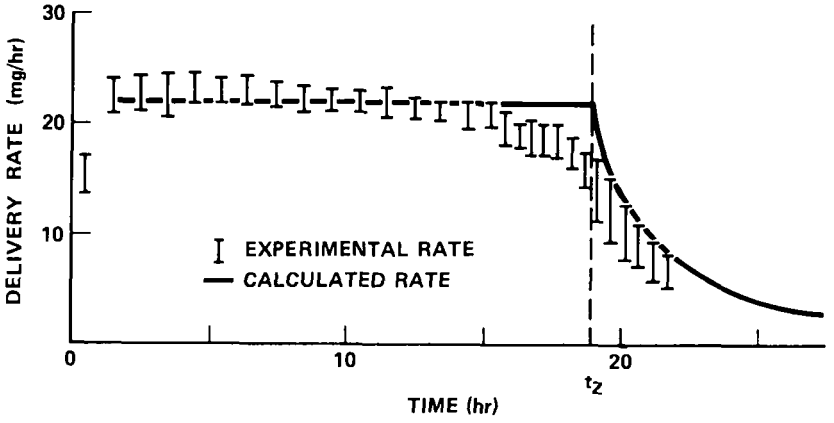


FIGURE 5
Comparison of in vitro and calculated release rates of potassium chloride from elementary osmotic pumps in water at 37°C[2].

## Release Rate In Vitro

The elementary osmotic pump system for indomethacin (EOP-indomethacin, Figure 7) has an 8-mm diameter and contains 85 mg of indomethacin as the sodium trihydrate salt. Systems were fabricated with release rates of 12, 9, and 7 mg/hr (designated 12/85, 9/85, and 7/85, respectively). The EOP-indomethacin was designed to be taken twice daily and to be therapeutically equivalent to 25 mg (q.i.d.) or 50 mg (t.i.d.).

At the start of this project, the therapeutic index for indomethacin was unknown, although it could be surmised that it would be narrow. Assuming that four doses per day is the ideal regimen and that 4 hours is the average half-life of excretion, it follows from equation 1 that the therapeutic index is about 3. The zero-order delivery rate, $Z_d = (dm/dt)_z$, was designed using equation 3:

$$Z_d = \left(\frac{dm}{dt}\right)_z = k \cdot \frac{A}{h} \cdot \pi_t \cdot S_d \qquad \text{Eq. 3}$$

where k is the membrane permeability, A is the area

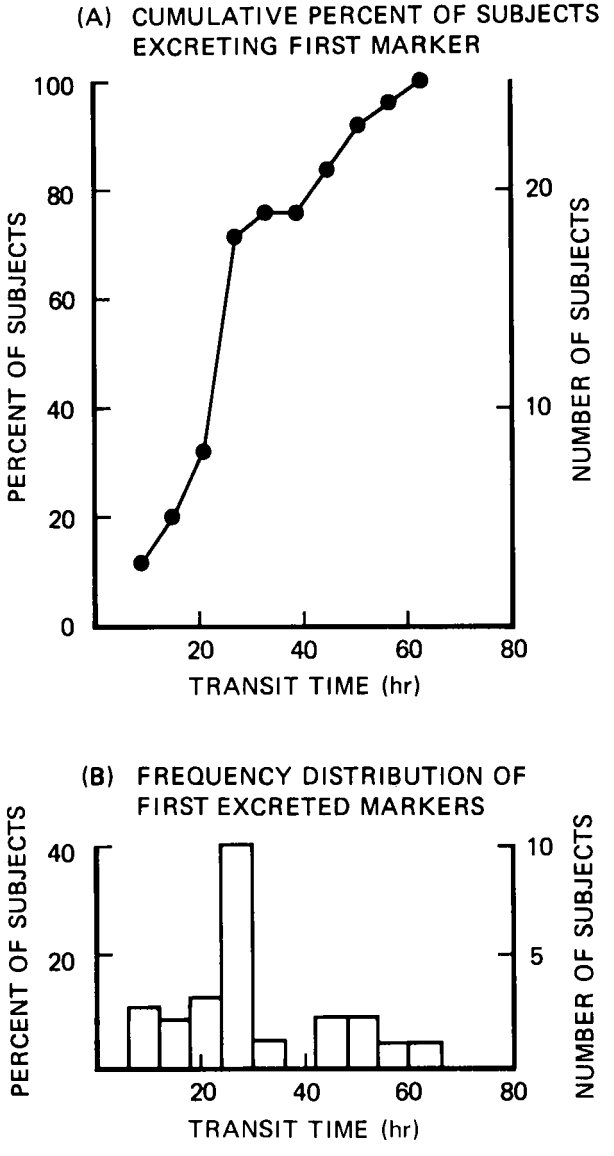


FIGURE 6
Mouth-to-anus transit time of inert objects in the gastrointestinal tract of man[3].

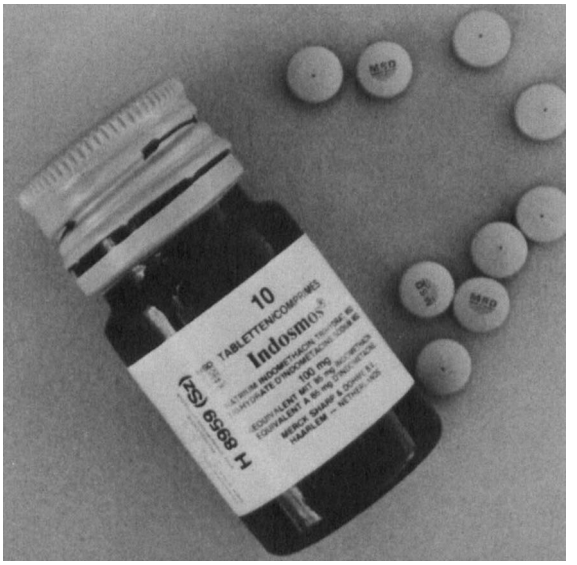


FIGURE 7
Osmosin™ tablet (EOP-indomethacin 7/85) and bottle.

of the membrane, h is the thickness of the membrane, $\pi_t$ is the total osmotic pressure in the core, and $S_d$ is the total drug solubility. The non-zero-order release rate profile is predicted from equation 4:

$$\frac{dm}{dt} = \frac{Z_d}{\left[1 + \frac{Z_d}{S_d \cdot V_t}(t - t_z)\right]^2} \qquad \text{Eq. 4}$$

where $V_t$ is the total volume inside the system and $t_z$ is the total time at which each system delivers at zero order. The physicochemical properties necessary to define the release rate profile were measured and are shown in Table 1.

Average release rate theoretically should be inversely proportional to membrane thickness or weight (Figure 8). Figures 9-11 show actual and theoretical release rate profiles from the three systems in USP intestinal fluid. These figures confirm that release

TABLE 1

Properties of Drug Core Determining Shape of Release Rate Profile

| Property | Symbol | Value |
|---|---|---|
| Mutual solubility of indomethacin sodium trihydrate | $S_d$ | 201.2 mg/ml |
| Total osmotic pressure | $\pi_t$ | 140.0 atm |
| Tablet core surface area | A | 1.6 $cm^2$ |
| Membrane density | $\rho_m$ | 1.3 g/ml |

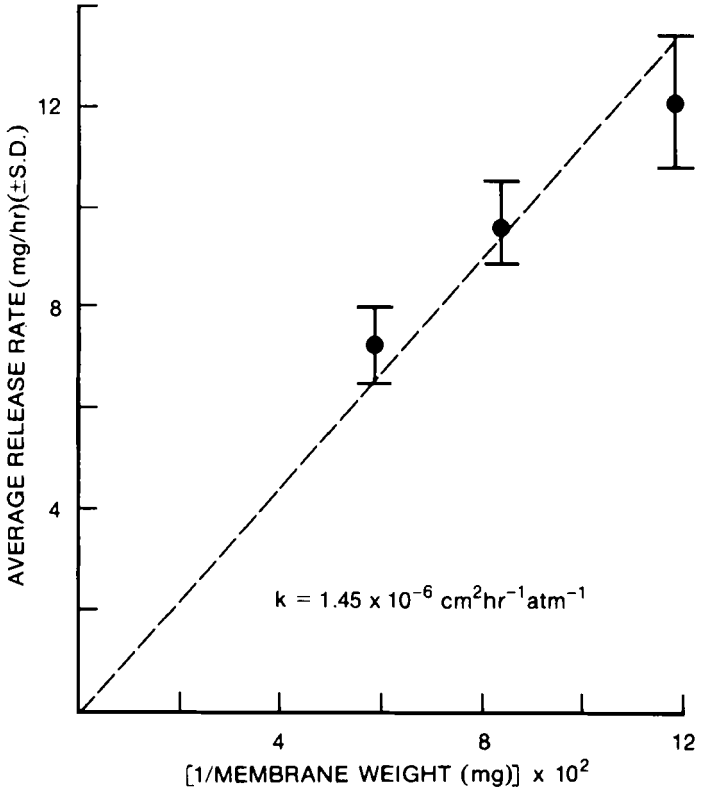


FIGURE 8
Relation between average release rate of drug from the EOP-indomethacin and weight of the membrane coating[4].

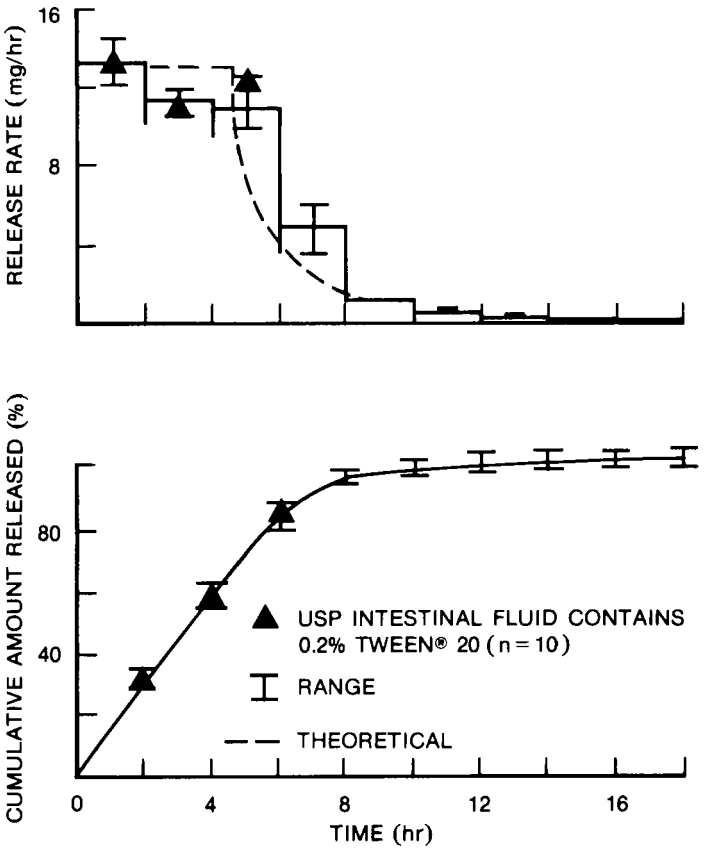


FIGURE 9
Release rate of indomethacin and cumulative amount released in vitro from the EOP-indomethacin 12/85 (n = 10)[4].

rate for the systems are predictable and independent of environment. The data show the rates in artificial gastric fluid for the first 4 hours and in intestinal fluid for subsequent times. The data indicated with triangles are the rates in intestinal fluid for the total time period.

Delivery Rate in the Gastrointestinal Tract

We have used the dog as a model for in vivo drug delivery since the dog's gastrointestinal tract

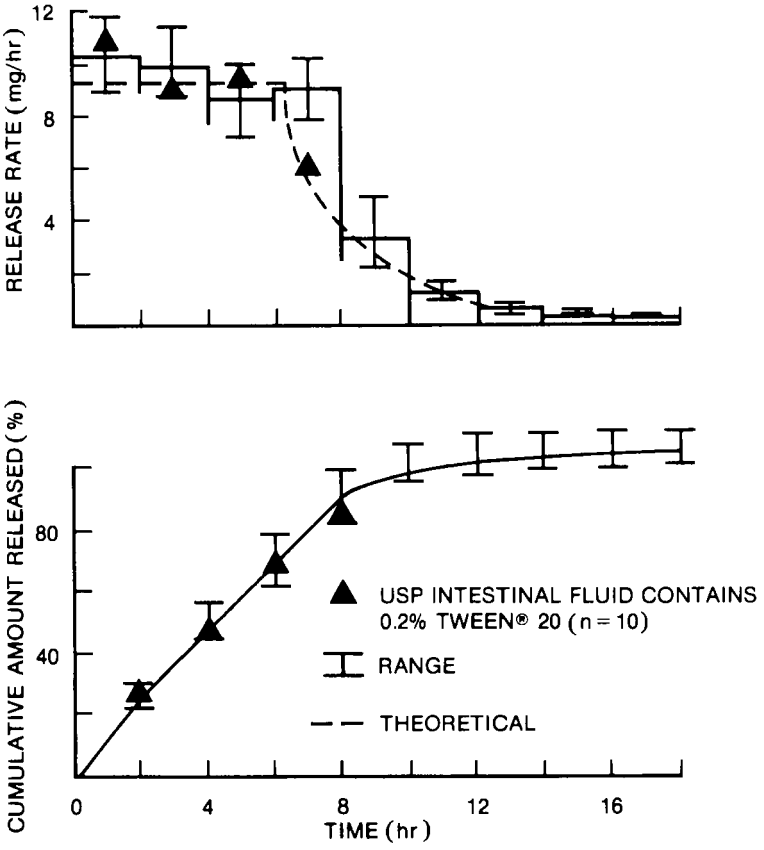


FIGURE 10
Release rate of indomethacin and cumulative amount released in vitro from the EOP-indomethacin 9/85 (n = 10)[4].

and motility patterns are similar to those of humans. As an example, Figure 12 compares cumulative amount release in vitro from the EOP-indomethacin 9/85 to cumulative amounts delivered into the gastrointestinal tract of several dogs. A series of marked dosage forms were given to a dog at regular intervals. Ten hours after the first dose, the dog was sacrificed and the dosage forms were retrieved from the gastrointestinal tract. The cumulative amount of indomethacin released from each system was determined by sub-

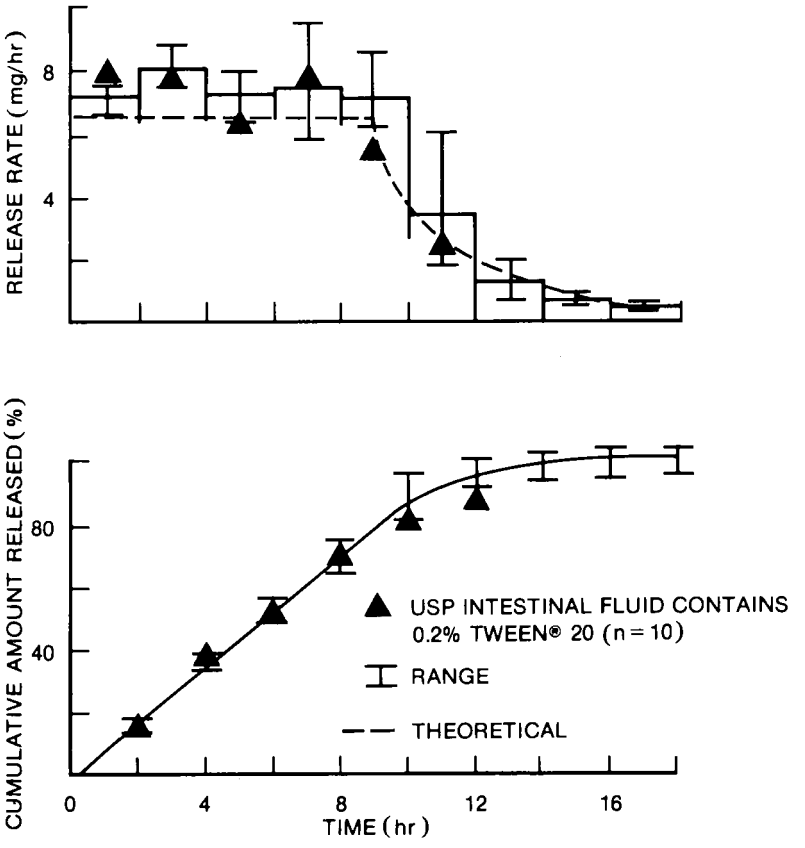


FIGURE 11
Release rate of indomethacin and cumulative amount released *in vitro* from the EOP-indomethacin 7/85 (n = 10)[4].

tracting the residual amount of drug found within each recovered system from the original drug content of each system. Figure 12 shows that the *in vivo* amounts released correspond closely with the *in vitro* results.

## Quality Control Testing of the Release Rate

Figures 13 and 14 show the average release rates and variations of the averages obtained with different test methods, including the USP basket and paddle

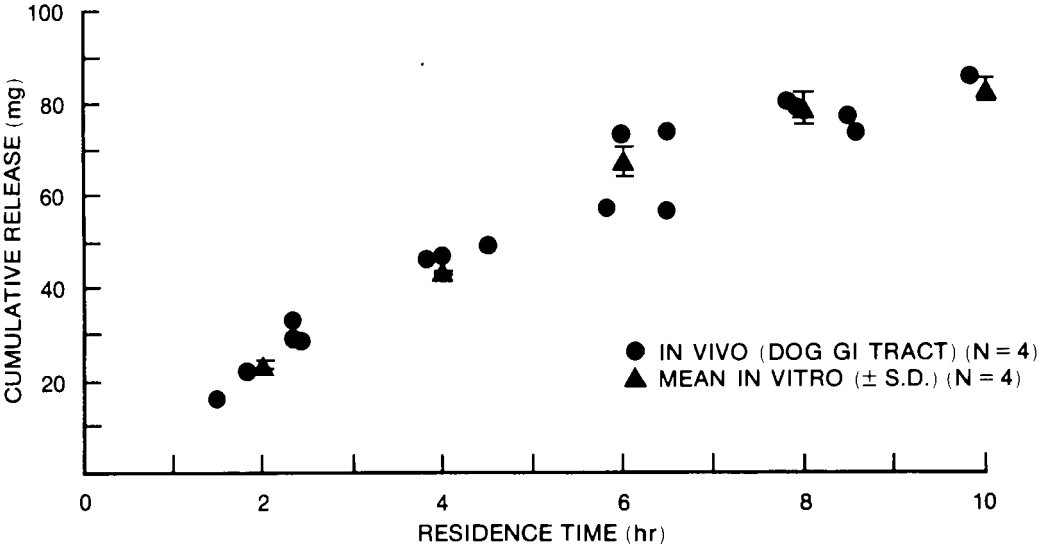


FIGURE 12
Comparison of cumulative amount of indomethacin released by the EOP-indomethacin 9/85 in vitro (n = 4) and amount released in the gastrointestinal tract of 4 dogs[4].

methods in simulated intestinal fluid at varying speeds of rotation. In the differential method one system each is submersed in separate test tubes for a set time period (e.g., 1 hour). Each hour all systems are transferred to another test tube via an automated process, and the content of the used test tubes are analyzed for drug content. These test tubes contain the hourly amounts released from each of the systems. This method also was used to measure the release rate profiles shown in Figures 9-11.

The average rate in Figures 13 and 14 is the same and independent of both method and stirring conditions. The in vitro release rate obtained with the USP basket and paddle methods and the differential method are the same as that observed in the gastrointestinal tract of the dog. We can thus view these methods as bioanalogous and meeting the criteria for

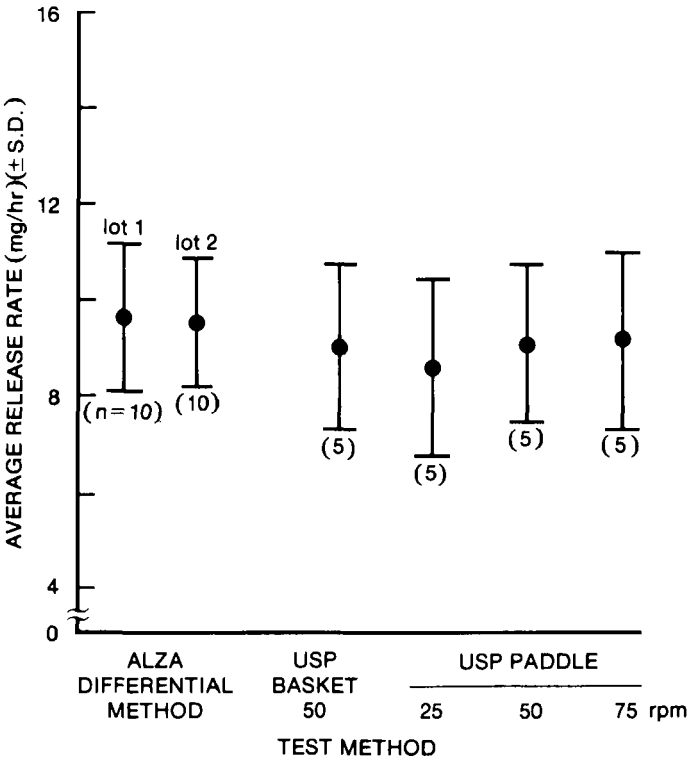


FIGURE 13
Average release rate from the EOP as a function of test method (I: S.D. within-system variation)[4].

valid quality control testing. These methods assure that the release rate profile measured for the lot will be the same as that obtained in an *in vivo* situation. The within-system variation is a measure of the flatness of the release rate profile during the zero-order period. The between-system variation is a measure of system to system variation of the average zero-order rate.

## Drug Absorption in Man[5]

The results of a preliminary single-dose bioavailability study showed that absorption of drug from the EOP-indomethacin 7/85, 9/85, and 12/85 was adequate.

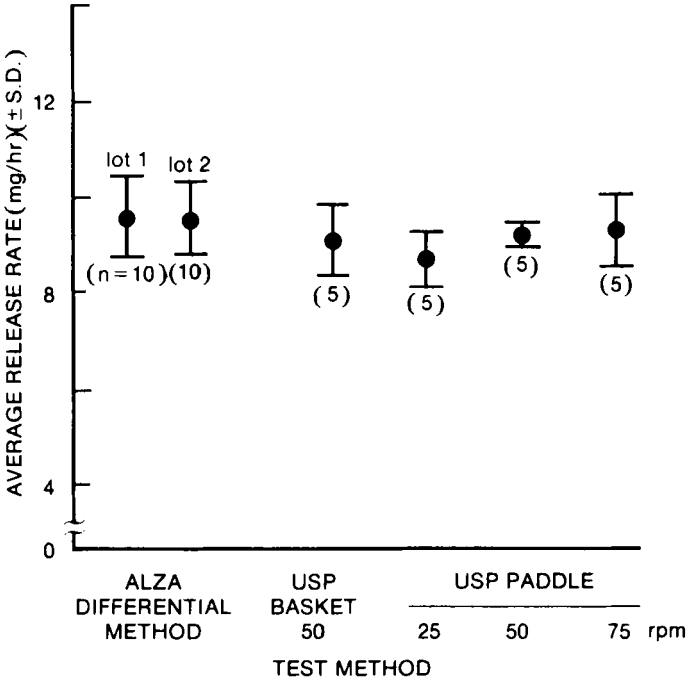


FIGURE 14
Average release rate from the EOP as a function of test method (I: S.D. between-system variation)[4].

Although the 12/85 system gave the highest extent of absorption, it was eliminated from subsequent trials because its control of plasma concentration was predicted to be inferior to that of the other two systems.

Absorption Rate--Fifteen healthy volunteers participated in a study to evaluate EOP-indomethacin 7/85, EOP-indomethacin 9/85, indomethacin capsules (3 x 25 mg), indomethacin capsules (25 mg at 0, 4, and 8 hr), and IV bolus (20 mg). Each subject received a different dosage form at 1-week intervals. Figure 15 shows average plasma concentrations in all 15 subjects for the EOP-indomethacin and the capsules. Rise in plasma concentration with the controlled-release dosage forms is much slower than that with the conven-

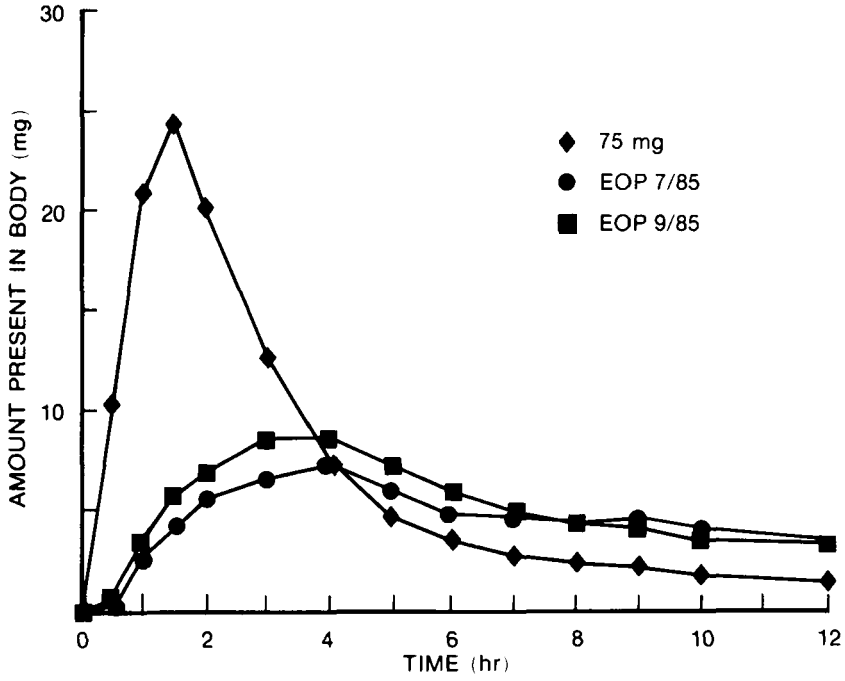


FIGURE 15
Comparison of plasma concentrations profiles in man following administration of EOP-indomethacin 7/85, EOP-indomethacin 9/85, and 3x25-mg (75 mg) indomethacin capsules.

tional capsules; however, from hours 6 to 12 after dosing, the plasma levels with the EOP are twice as high. Three capsules given as a single dose produce a plasma concentration profile characterized by a rapid peak followed by a rapid decline as absorption nears completion. This figure shows the absence of dose dumping from the EOP.

Figure 16, which compares EOP-indomethacin 7/85 and 9/85 with the indomethacin bolus, reveals an oscillating plasma concentration profile for the bolus dosage form. Consistent with the dosing time at t = 0 and t = 8 hr, the peak expected at t = 4 hr appears in the individual subject data; however, it

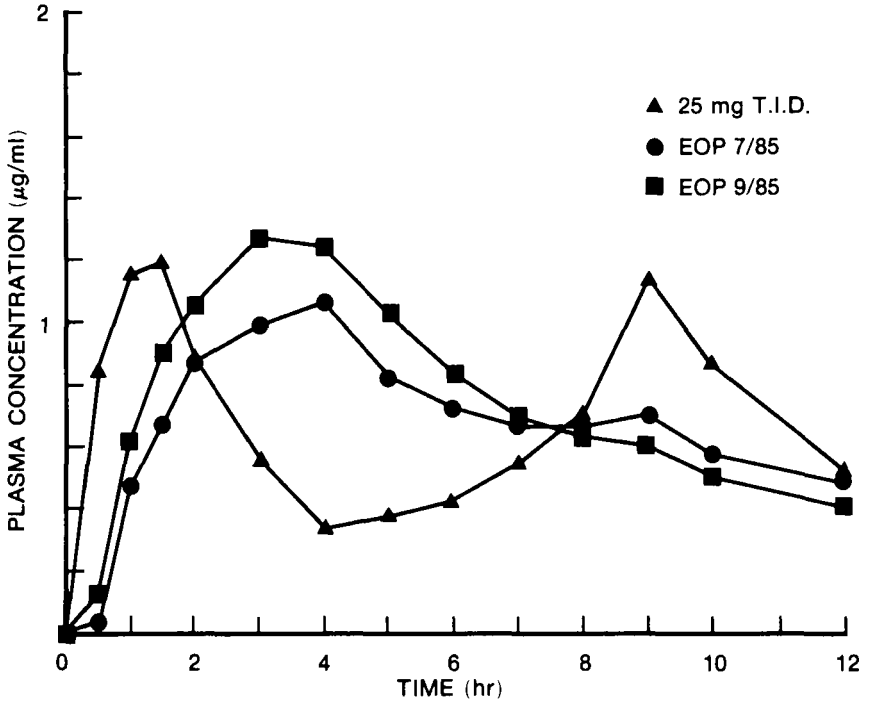


FIGURE 16
Plasma concentration profiles in man following administration of EOP-indomethacin 7/85, EOP-indomethacin 9/85, and 25-mg indomethacin capsules (t.i.d.).

disappears when the overall subject data are averaged. EOP-indomethacin demonstrates, in contrast, a more constant plasma profile.

The actual amount of drug absorbed by the body at any time can be calculated from the amount of drug in the body and the amount excreted at that time using the Loo-Riegelman technique[6]. Figure 17 plots the cumulative amounts absorbed for the regimens using this technique. The data verify the results of Figures 15 and 16, which show that 75 mg from capsules is rapidly absorbed during the first 4 hours. Since indomethacin undergoes entero-hepatic recirculation, the actual amount absorbed from the 75-mg dose given as capsules is 100 mg because some of the

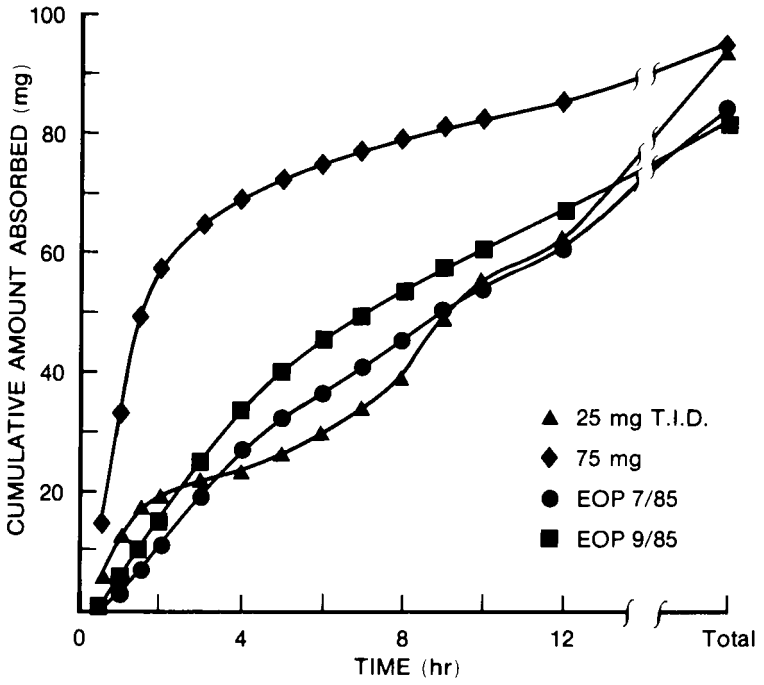


FIGURE 17
Cumulative amount of indomethacin absorbed from the gastrointestinal tract following administration of the EOP-indomethacin 7/85 and 9/85, and 25-mg (t.i.d.) and 3x25-mg indomethacin capsules.

drug reappears in the plasma. This finding also holds for the other dosage forms. Capsules containing 25 mg of drug administered every 4 hours have a more linear absorption profile. Initial absorption rates during the first 4 hours are exactly 7 mg/hr and 9 mg/hr for the EOP-indomethacin 7/85 and 9/85, respectively. Beyond the initial period, the capacity of the gastrointestinal tract to absorb the drug at the delivered rate appears to drop[5] and drug continues to be absorbed at a controlled rate equivalent to 85% of that absorbed from a bolus dose.

Steady State Plasma Concentrations--The average plasma concentrations and the degree of fluctuation

present at steady state were defined in an open, randomized, crossover study conducted in 12 healthy volunteers[7]. EOP-indomethacin 7/85 and 9/85 were administered twice daily; indomethacin capsules (25 mg) were given at 0, 4, and 8 hours and 3x25 mg at 12 hours. Indomethacin capsules (50 mg) were administered at 0, 4, and 14 hours. All dosage forms were given for 5 days followed by a 9-day washout period. Plasma concentrations were measured at frequent intervals during the first 12 hours, at subsequent 24-hour intervals just prior to the next dosing, and at detailed time periods during steady state on the fifth day.

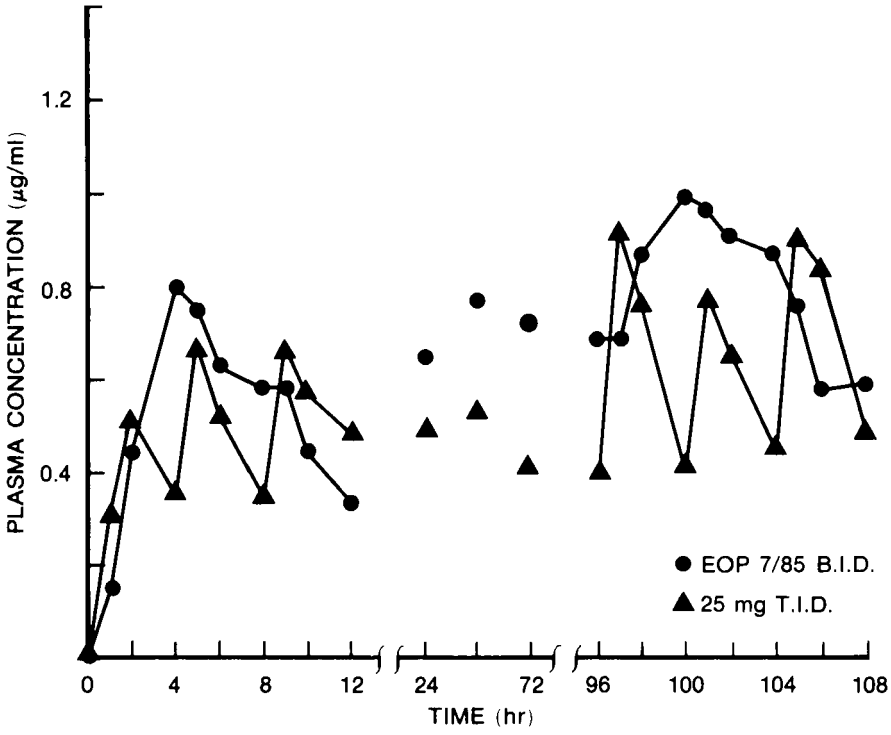


FIGURE 18
Mean indomethacin plasma concentrations after multiple doses of EOP-indomethacin 7/85 (b.i.d.) and 25-mg indomethacin capsules (t.i.d.)[7].

Figures 18 and 19 show that oscillations in plasma concentrations are smaller with the EOP-indomethacin than with either of the capsule dosage regimens and that the minimum plasma concentrations of indomethacin over time are higher with the controlled-release systems. Figure 20 shows the predose plasma levels of EOP-indomethacin 7/85 and 25-mg indomethacin capsules during days 2-5. With the EOP-indomethacin, average plasma concentrations at steady state are almost twice that of capsules ($p<0.01$). Fluctuations in plasma concentrations can be calculated from the average plasma concentration at steady state and its oscillation pattern. Figure

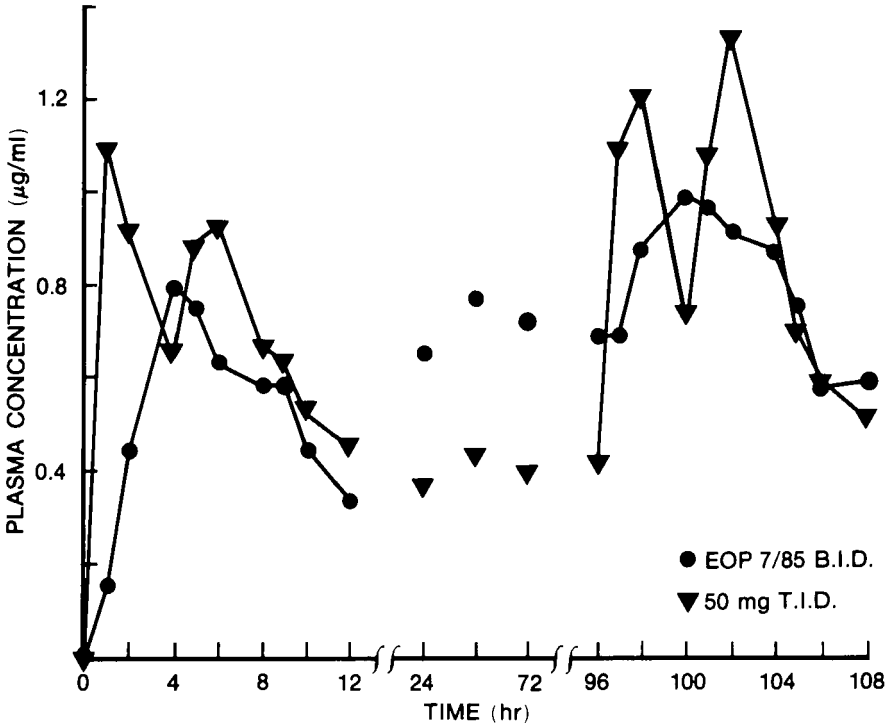


FIGURE 19
Mean indomethacin plasma concentrations after multiple daily doses of EOP-indomethacin 7/85 (b.i.d.) and 50-mg indomethacin capsules (t.i.d.)[7].

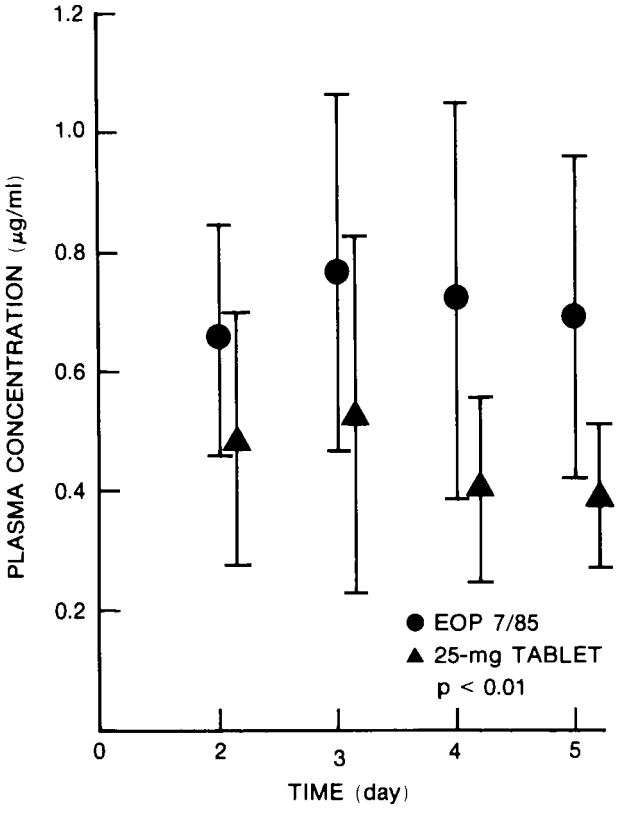


FIGURE 20
Pre-dose (0 hr) plasma levels of indomethacin following administration of EOP-indomethacin 7/85 and 25-mg indomethacin capsules during multiple-dose study.

21 shows the average deviation from the mean 12-hour steady state level on day 5. Fluctuations for the different dosage forms show significant differences; the smallest fluctuations occurred with the EOP-indomethacin 7/85.

These results suggest that EOP dosage forms achieve a high degree of control that is consistently superior to capsule regimens in constancy of drug release and magnitude of plasma concentrations at dosing time.

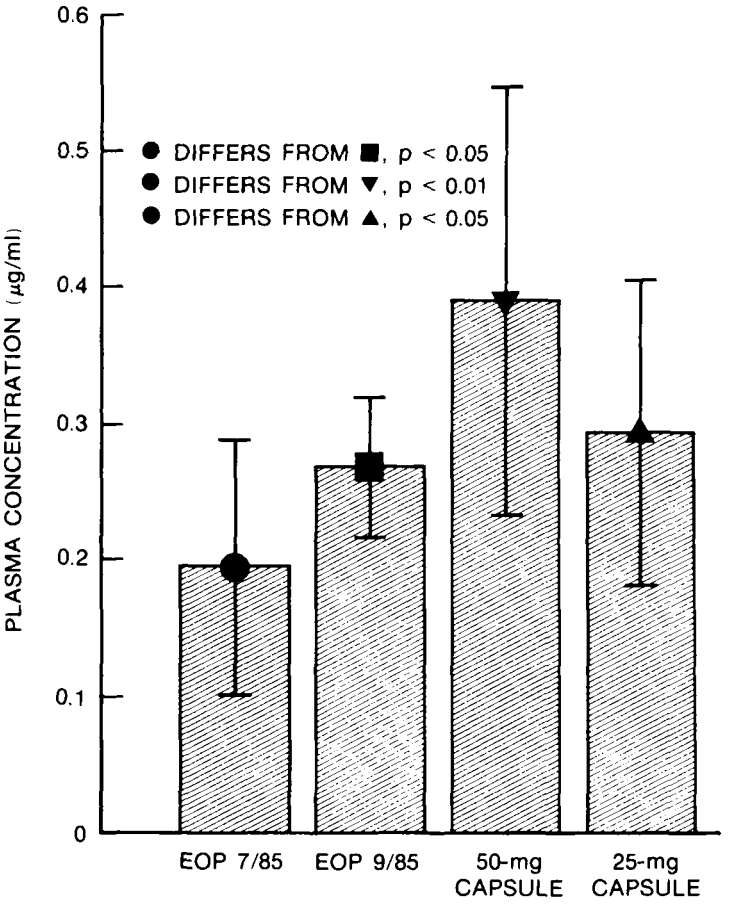


FIGURE 21
Average deviation from the mean at 12 hr following administration of EOP-indomethacin 7/85 and 9/85, and 25- and 50-mg indomethacin capsules.

Clinical Testing--In clinical trials, the EOP-indomethacin 9/85 exhibited a somewhat higher degree of side effects than the EOP-indomethacin 7/85, and therefore all subsequent clinical data reported here were carried out with the EOP-indomethacin 7/85 (available in the U.K. under the trademark OSMOSIN™).

A 12-week double-blind, randomized multi-center study[8], conducted with 402 outpatients with osteoarthritis of the knee, compared the EOP-indomethacin

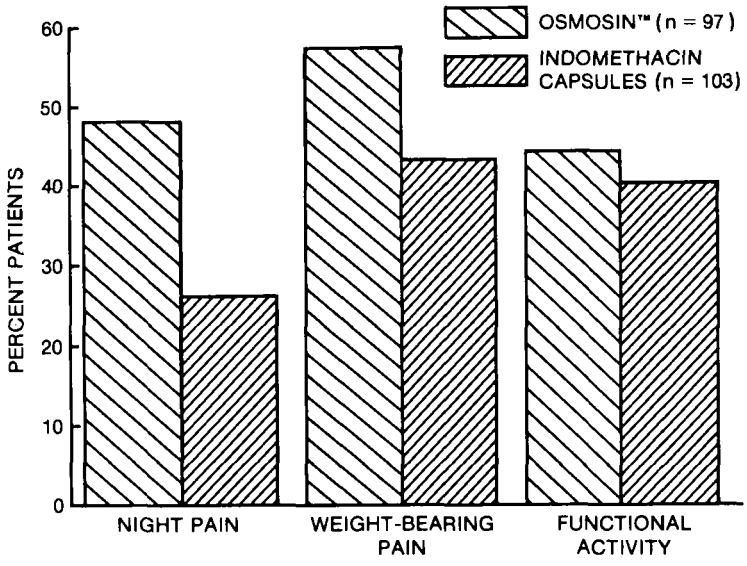


FIGURE 22
Percentage of patients with appreciable clinical improvement in night pain, weight-bearing pain, and functional activity during therapy with Osmosin™ tablets (EOP-indomethacin 7/85) and 25-mg indomethacin capsules[9].

7/85 with 25-mg capsules. In this study one EOP-indomethacin 7/85 (q.d.) was compared with one 25-mg indomethacin (t.i.d.) capsule; also one EOP-indomethacin 7/85 (b.i.d.) was compared with two 25-mg indomethacin capsules. Both pairs of regimens compared equal quantities of drug.

Results of the study showed that approximately 77% of the patients were maintained on one EOP-indomethacin 7/85 a day. Figure 22 shows that the EOP-indomethacin 7/85 is at least as effective as the capsules in suppressing night pain, weight-bearing pain, and functional activity. Patients and physicians rated the osmotic system at least as effective as conventional capsules (Figure 23).

In a separate 3-week double-blind, randomized multi-center study among 194 patients with osteoar-

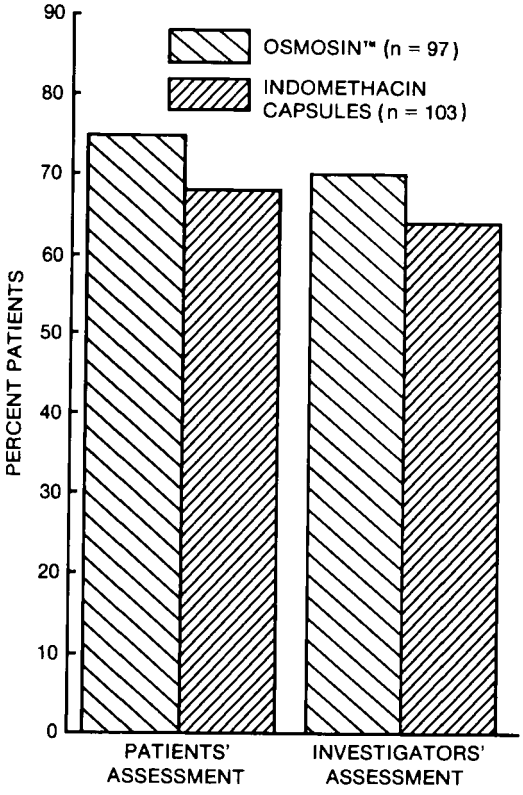


FIGURE 23
Patients' and investigators' assessment of patients with good to excellent rating during therapy with Osmosin™ tablets (EOP-indomethacin 7/85) and 25-mg indomethacin capsules[9].

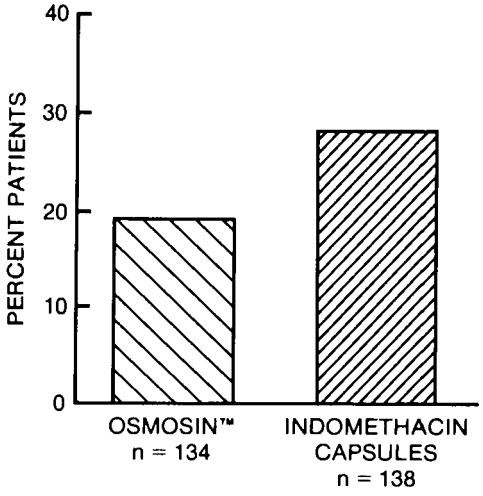


FIGURE 24
Percentage of patients experiencing central nervous system side effects during therapy with Osmosin™ tablets (EOP-indomethacin 7/85) and 25-mg indomethacin capsules[9].

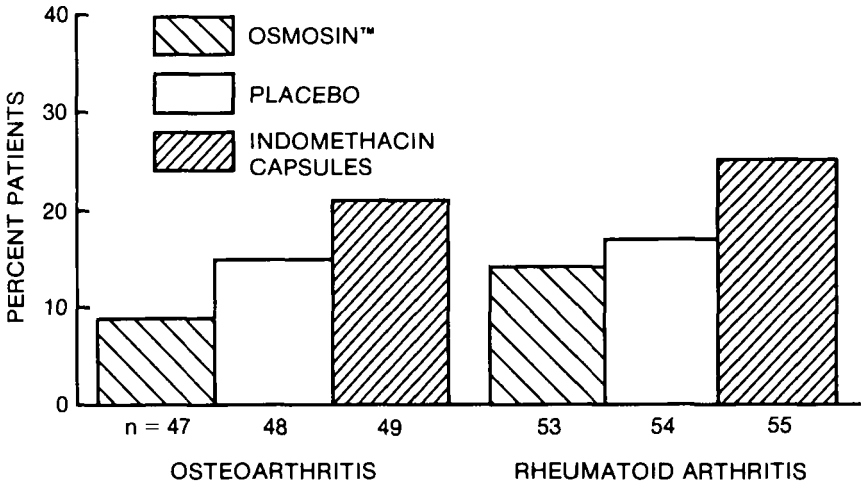


FIGURE 25
Percentage of patients with osteoarthritis and rheumatoid arthritis experiencing gastrointestinal side effects during therapy with Osmosin™ tablets (EOP-indomethacin 7/85), 25-mg indomethacin capsules, and placebos[9].

thritis of the knee, the osmotic system reduced CNS and gastrointestinal side effects compared with the conventional therapy (Figures 24 and 25)[9]; in addition, gastrointestinal side effects were as mild as with placebos.

## CONCLUSIONS

1. The delivery rate of a controlled-release dosage form is a therapeutically significant parameter that must be controlled just as the quantity and the purity of the chemical compound are controlled to certify therapeutic response. This delivery rate needs to be controlled *in vivo* and tested in bioanalogous variable conditions prevailing in the gastrointestinal tract.
2. The optimal rate-controlled dosage form should exhibit maximum rate control and provide sufficient

extent of absorption. In contrast, bolus dosage forms often exhibit a high extent of absorption but minimal rate control.

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