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A COMPARISON OF IN VIVO AND IN VITRO METHODS OF STUDYING THE RELEASE RATE OF DRUG INTO THE GASTROINTESTINAL TRACT IN MAN EXEMPLIFIED BY SUSTAINED RELEASE FORMULATIONS OF PHENDIMETRAZINE.

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ABSTRACT

An analogue computer system was used to simulate a model representing the metabolism and excretion of phendimetrazine and its metabolites, phenmetrazine and phendimetrazine-N-oxide. This model was used in connection with an analogue computer program to compute the rate of release of phendimetrazine into the gut lumen from three sustained release formulations of phendimetrazine using data obtained by analysis of plasma or urine. The dosage form availability profile so obtained was compared with in vitro dissolution test data.

The in vitro method was found to predict a rate of release substantially greater than that found in vivo.

INTRODUCTION

There is a growing belief that in vitro methods of studying the rate of release of a drug from a formulation are physiologically unsound and clinically misleading. To investigate this matter we

have studied three formulations of phendimetrazine using an analogue computer to calculate the rate of release in vivo using urine and plasma drug concentration data, and compared it with an in vitro technique based on NF XIV.

SUBJECTS AND DRUGS

Phendimetrazine tartrate (105 mg) in solution was administered orally to three subjects and also a dose of 70 mg to one of them. Phendimetrazine (32.7 mg) was given intravenously to one subject.

Phenmetrazine hydrochloride 25 mg in solution was administered orally to the same three subjects and intravenously to one of them. Conditions of acid urine were produced by administration of ammonium chloride (Beckett and Tucker 1966)[1]. Collection of urine and blood samples and sample analysis for both drugs and metabolites were described by Beckett and Raisi (1976 a, b, c)[2].

Three different formulations of phendimetrazine A, B, C each containing 105 mg of phendimetrazine tartrate, were administered to two subjects. These preparations used membranes around pellets through which the drug diffuses - the Goldbec process.

COMPUTER SYSTEM

Two analogue computers; A pace TR20R (Electronic Associates Ltd.) and an EAL 180 were interfaced together and used in conjunction with an x - y recorder (Advance Electronics Ltd.).

Analogue computer programming was done by standard methods (Mausner 1971)[3]. Examples of the application of this technique to the simulation of pharmacokinetic systems have been given by Mikailova and others 1974[4], Wilkinson and Beckett 1968[5] and the general assumptions

underlying the use of compartmental models to investigate the absorption and elimination of drugs listed by Beckett and Tucker 1968.[6]

The processes of absorption distribution, metabolism and excretion were assumed to follow first order kinetics. The process of absorption was assumed to be faster than the other processes and was assigned the arbitary value of 1000; all other microrate constant values were related to it.

METHOD OF IN VIVO ESTIMATION OF DRUG RELEASE RATE

The Technique

Stelmach et al (1965)[7] described an analogue computer program which uses blood concentration/time data to compute the amount of drug released from a formulation of that drug into the gut lumen as a function of time; the dosage form availability versus time (DFAT) profile. This program requires that a suitable pharmacokinetic model be found which simulates the absorption, metabolism and excretion of the drug in question.

The method of Stelmach was used with the following modifications:

1. The plasma concentration time data as input was provided by a variable diode function generator instead of a curve follower; this aids differentation accuracy as there is less noise.
2. When the plasma concentration information was not available, the urine excretion rate data of parent phendimetrazine was used instead as the rate of excretion is proportional to plasma concentration under the acid urine conditions employed.

Obtaining the model to simulate the pharmacokinetics of phendimetrazine

In man, phendimetrazine, an anoretic agent, gives under conditions of acidified urine, two metabolites; phendimetrazine N - oxide and phenmetrazine, which are excreted in the urine in amounts accounting for 20% and 30% of the administered dose respectively together with 30% unchanged drug (Beckett and Raisi 1977 c)[2]. Since one of the metabolites, phenmetrazine, is itself a well known anorectic, it was possible to administer it both orally and intravenously and thus to study it separately.

When phenmetrazine was given orally to man, 65% of the administered dose was recovered as unchanged drug in the urine (Beckett and Raisi, 1976 b)[2].

After trial of a large number of possibilities, it was found that two compartment models best represented the pharmacokinetics of phendimetrazine and phenmetrazine, and a single compartment the kinetics of the polar phendimetrazine N - oxide.

The composite model is depicted in Figure 1. Such a model is consistent with the known properities of the compounds; both PD and PM being lipid soluble, whereas the N - oxide is a polar metabolite. All processes of absorption, metabolism and distribution were assumed to follow first order kinetics. The two compartment model selected to simulate the pharmacokinetics of phenmetrazine, which forms a sub-system of the model depicted in Figure 1, was first investigated by administering phenmetrazine itself. Following the administration of phenmetrazine in solution, the urine and plasma were analysed for phenmetrazine. A good fit was obtained for both cumulative urine excretion curves as well as for the rate of excretion against time curves following oral drug administration. However, it

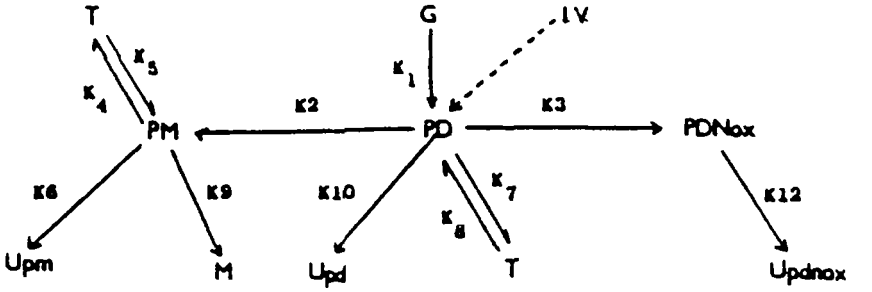

FIGURE 1

Compartmental model for the metabolism and excretion of phendimetrazine and its metabolites, phenmetrazine and phenmetrazine N - oxide, following oral and intravenous dosing with phendimetrazine.

The two compartment model representing phenmetrazine is incorporated into this model.

PD	-	Phendimetrazine inner compartment
PM	-	Phenmetrazine inner compartment
PDNox	-	Phendimetrazine N - oxide single compartment
U_{pd}, U_{pm}, U_{pdnox}	-	Urinary excretion of phendimetrazine, phenmetrazine and phenmetrazine N - oxide
M	-	Unknown other metabolites of phenmetrazine
T	-	Tissue compartments
K_{1-12}	-	First order rate constants

was found necessary to multiply the plasma concentration by a factor of 3.5 to obtain a fit for the computer predicted inner compartment concentration because the inner compartment represents extracellular fluid as well as plasma. Extracellular fluid volume to plasma volume ratio is expected to be about 4 - see for example, Ganong.[8] The same model was found to simulate the pharmacokinetic processes following an intravenous dose of phenmetrazine, typical curves for urine cumulative and rate of excretion data are shown in Figure 2a. Following the

FIGURE 2

Obtaining the model: Analogue computer generated curves using the scheme of Figure 1 and the corresponding experimental data following administration of the compounds in solution or i.v.

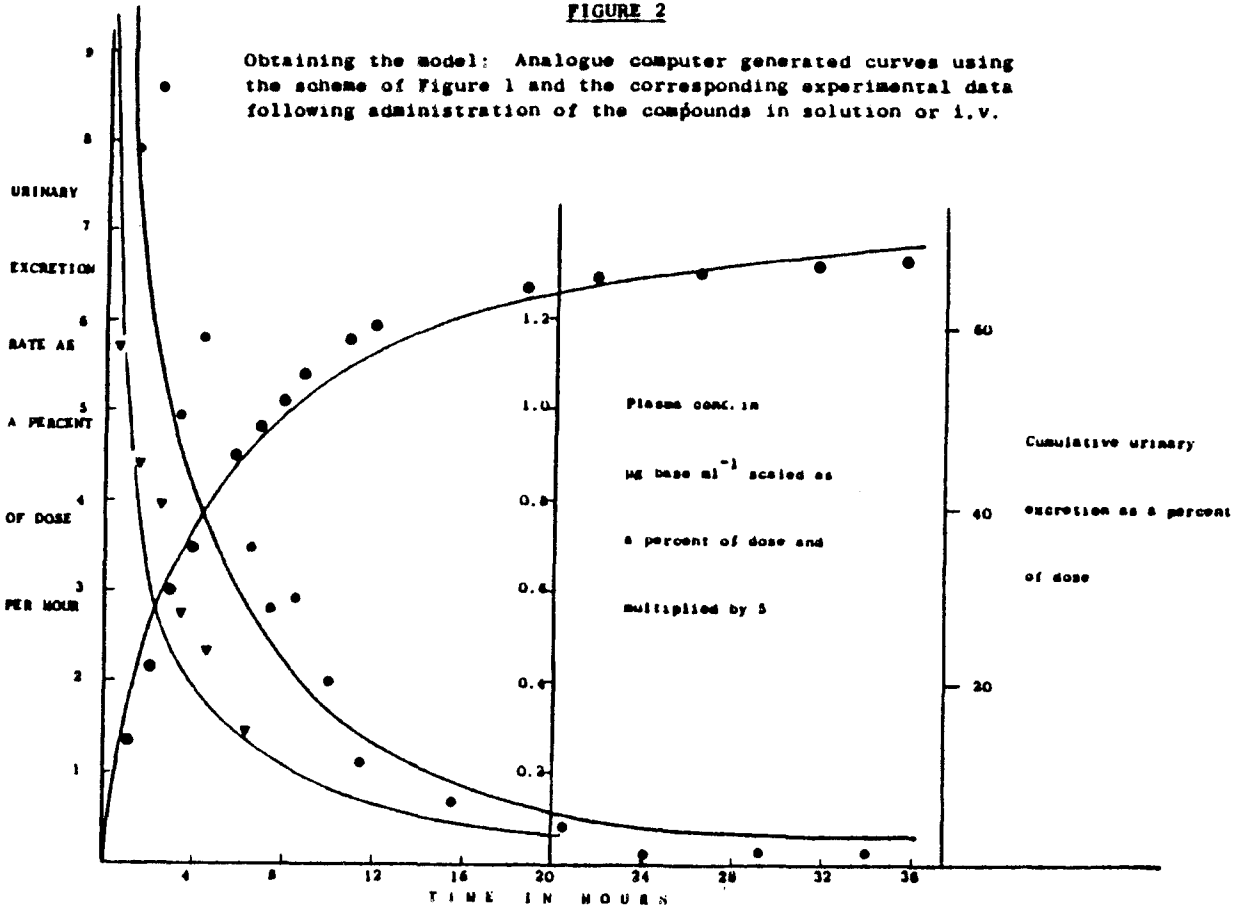

FIGURE 2a Fitting of analogue computer generated curves to experimental data for the rate of excretion and cumulative excretion of phenmetrazine following intravenous dosing with 25 mg.

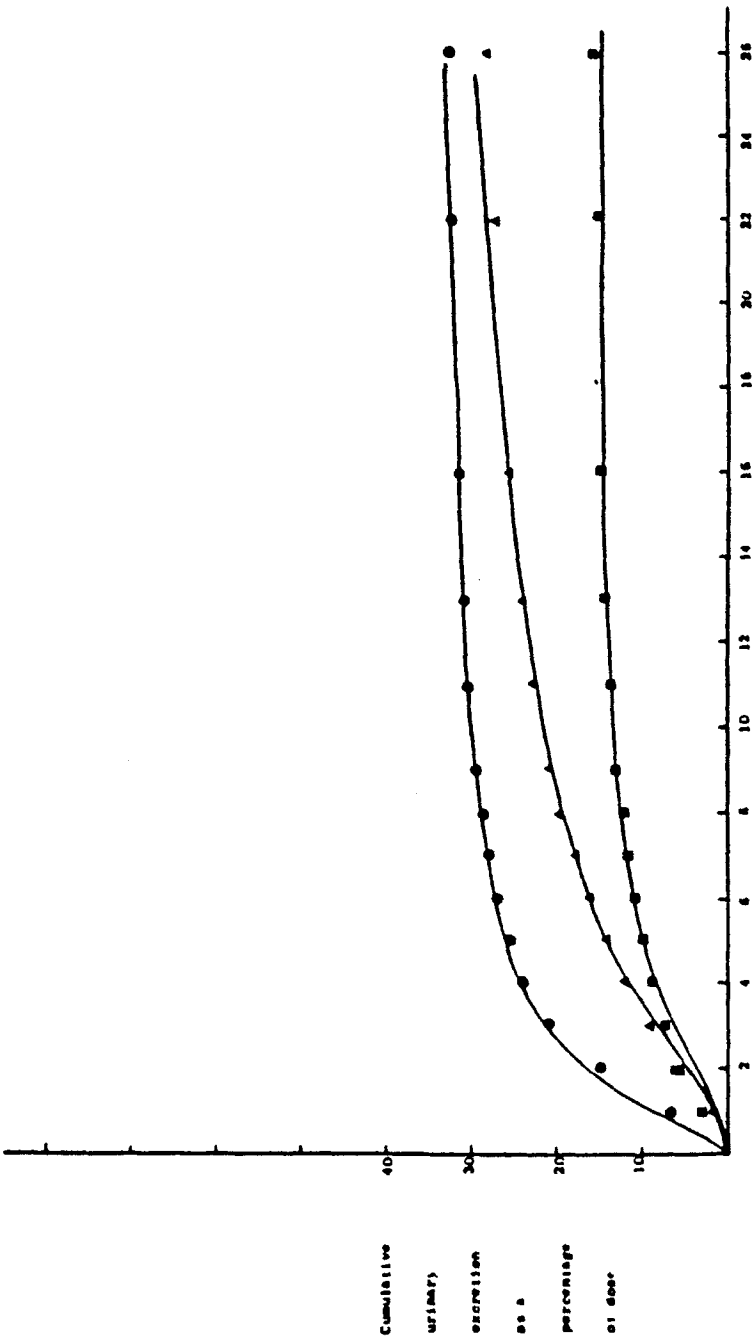

FIGURE 2b Comparison of analogue computer generated curves and experimental data for the cumulative excretion of phendimetrazine, phenmetrazine and phendimetrazine N-oxide following dosing with 105 mg phendimetrazine tartrate, subject 3. ■- phendimetrazine N-oxide, ▲- phenmetrazine, ●- phendimetrazine.

administration of phendimetrazine in solution to three subjects orally and intravenously to one of them, the urine was analysed for parent drug and the two metabolites. Using the model in Figure 1, the analogue computer generated curves which gave a close correspondence to the points representing cumulative excretion and rate of excretion (see Figure 2b). The microrate constants for the model are given in Table 1. Following the intravenous trial, close correspondence was again obtained for cumulative and rate of excretion/time data.

The inner compartment following PD administration was again found to represent extracellular fluid and so necessitated multiplication of the plasma concentration by the extracellular fluid/plasma volume ratio - 3.5.

METHOD OF IN VITRO ESTIMATION OF DRUG RELEASE

The in vitro data was supplied by the manufacturers and was obtained using the basic procedure of the NF XIV, but with the following modifications in the apparatus: the rotating shafts were in an incubator oven instead of a water bath, and the speed of rotation was 28-30 r.p.m. instead of 40 $\pm$ 2 r.p.m. Samples equivalent to 3 capsules (3 x 105 mg) of phendimetrazine tartrate were used. Release was determined in 200 ml bottles containing 150 ml of digestive fluid; this method enables one to choose a convenient sample size without suppressing the release rate by a saturation effect. The digestive fluid (prewarmed to 37°C) for the first hour was simulated gastric fluid, pH 1.5 and from the second to the eighth hour was simulated intestinal fluid with pH which varied progressively from 4.5 to 7.5 during the period.

After the eighth hour, the residual pellets and all the fluids collected at the appropriate time intervals were made alkaline, extrac-

TABLE 1

Analogue computed values for the first order rate constants for absorption, metabolism, distribution and excretion of phendimetrazine and its metabolites

The rate constants refer to the scheme shown in Figure 1

Rate Constants	SUBJECTS				
	1	1	2	3	3
	IV 33 mg	Oral 105 mg	Oral 105 mg	Oral 105 mg	Oral 70 mg
K1	-	1000	1000	1000	1000
K2	310	405	221	423	364
K3	190	139	200	150	150
K4	342	342	154	208	185
K5	009	009	016	016	018
K6	225	225	272	272	273
K7	700	277	798	602	602
K8	250	115	332	249	259
K9	095	073	035	072	072
K10	211	211	323	333	339
K12	720	720	665	702	702

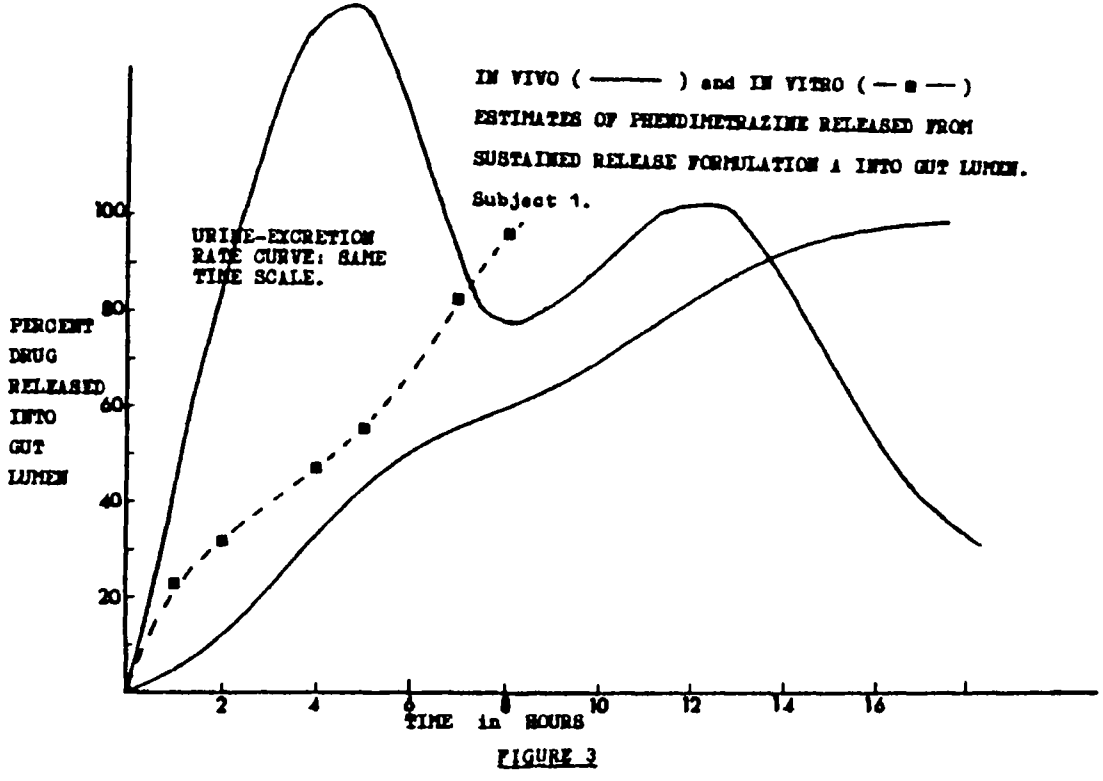

FIGURE 3

In vivo (——) and in vitro (— ■ —)
Estimates of Phendimetrazine released from sustained release formulation A into gut lumen: Subject 1.
Urine excretion rate curve is shown on the same time scale.

ted with chloroform and the extracts were assayed for phendimetrazine, by non-aqueous titration with standard perchloric acid-glacial acetic acid, using crystal violet as the indicator.

Using the model to investigate sustained release formulations of phendimetrazine

Three different sustained release formulations of phendimetrazine tartrate A, B and C, each containing 105 mg, were administered to two subjects under acid urine conditions. Formulations A and B were administered only to subject 2 but formulation C was given to

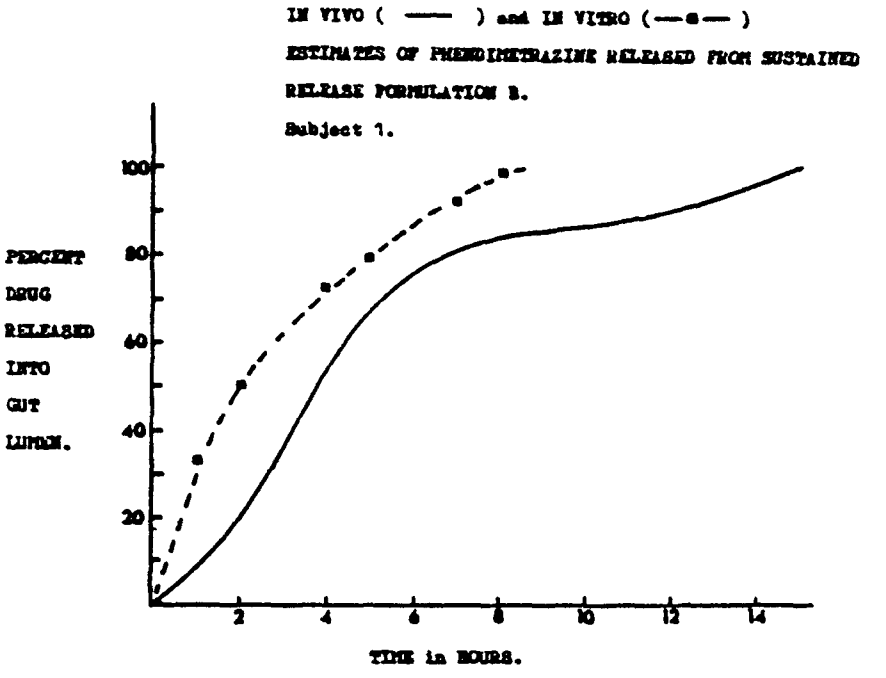

FIGURE 4

In vivo (——) and in vitro (— ▪ —)
Estimates of Phendimetrazine released from sustained release formulation B: Subject 1.

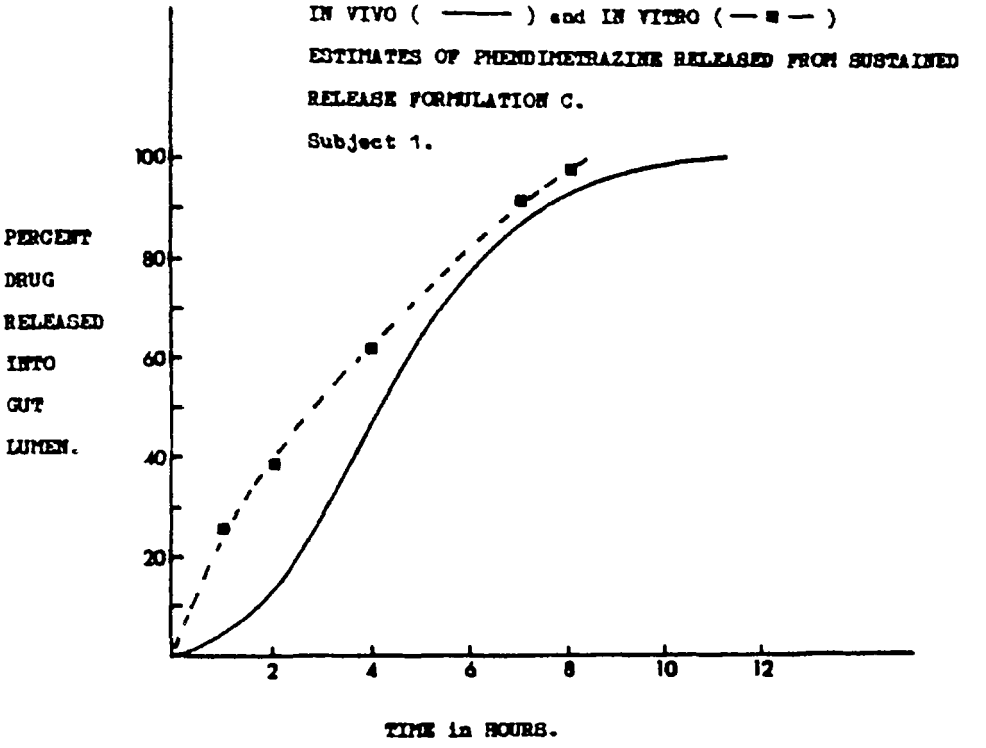

FIGURE 5

In vivo (——) and in vitro (—■—)
Estimates of Phendimetrazine released from sustained release formulation C: Subject 1.

both. The urine was analysed for parent drug and its two metabolites as before.

A variable diode function generator with variable break points was programmed to simulate the plasma concentration/time plot of phendimetrazine when this was available or the urine rate of excretion/time plot when it was not. Conceived as a graph, the voltage output of this device is proportioned to the y axis value at a time t and was used to provide the inner compartment concentration for simulating

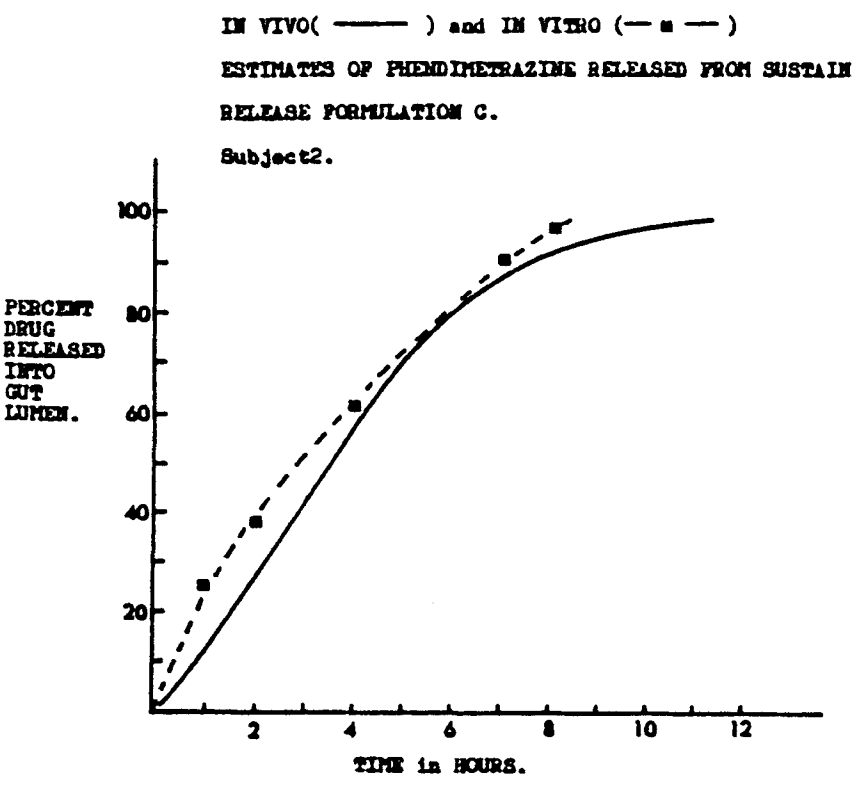

FIGURE 6

In vivo (———) and in vitro (— ■ —)
Estimates of Phendimetrazine released from sustained release formulation C: Subject 2

distribution, metabolism and excretion after doses of sustained release PD.

Having programmed the VDFG, the computed curves were then fitted to the experimental points for the drug and its metabolites obtained following doses of sustained release PD using as program parameters the microrate constants given in Table 1 obtained using aqueous solution. In this manner, a model was obtained which satisfactorily des-

cribed the processes of distribution metabolism and excretion following a dose of sustained release PD as evidenced by a satisfactory fit between the computer generated curves and the points representing excretion data. This model was then used unchanged in connection with the program for computing the dosage form availability time profiles.

For each of the four trials, three different formulations in one subject and one in another, a curve was obtained which shows the percentage of drug released from the formulation into the gut lumen as a function of time. These curves are given in Figures 3, 4, 5 and 6.

RESULTS

The in vivo dosage form availability time profiles obtained by use of the analogue computer technique based on Steimach's system but extended from the simple single compartment without metabolites he described to the complex scheme of Figure 1, are given for the three sustained release formulations in Figures 3 - 6. For comparison, the in vitro dissolution data obtained from the modified NF XIV method described above, is given on the same graphs.

The small intersubject variation of the in vivo technique is shown by comparison of Figures 3 and 4, where formulation C has been given to two different subjects. In every case the in vitro technique gives a shorter time scale.

Comparison of these in vitro and in vivo curves show that one hour in the rotating basket is equivalent to a longer time in the body; almost two hours in formulations A and B and brings into question the clinical relevance of the official dissolution tests which may be unphysiological in their severity.

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