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GASTRO-INTESTINAL BIOAVAILABILITY ASSESSMENT OF COMMERCIALY PREPARED SUSTAINED-RELEASE LITHIUM TABLETS USING A DECONVOLUTION TECHNIQUE

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ABSTRACT

The bioavailability of a commercial formulation of sustained release Lithium, containing 10.4 mM in the form of carbonate per tablet, was evaluated by a bioequivalency assay using 10 healthy volunteers. As reference, gelatine capsules containing the same dosage were used. By numerical deconvolution of the mean urinary excretion curves an equation representing the amounts of Lithium released in the gastrointestinal tract was obtained, proving equal to $1.0 + 0.94.t - 0.012.t^2$, $0 \leq t \leq 8$ hours. This results were confirmed by the Bayesian interpretation of the bioequivalency study, with acceptability intervals determined for each parameter used, total amount of lithium excreted in the urine and maximum urinary excretion rate. The limits were established from the curves obtained under simulation using the absorption-disposition parameters of the urinary excretion curve and optimum gastrointestinal release kinetics. The results suggest that the bioavailability of the tablets is moderately reduced as the result of the release rate being lower than the optimum value.

The correlation between the amounts dissolved in vitro using the rotating basket at 100 rpm and HCl 0.1 N as solvent and the amounts released in vivo estimated by numerical deconvolution was excelent.

INTRODUCTION

The pharmacokinetic models hitherto used to design and evaluate sustained-release pharmaceutical dosage forms (1,2) have considerable limitations, sometimes being based only on a monocompartimental model at others, necessitating resolution of a highly-complicated multicompartimental model, not always possible from the information provided by the plasma-level time or urinary excretion curves.

In recent years the theory of linear models has been generally applied in pharmacokinetics and biopharmaceutics. Cutler (3) specifically discusses the use of deconvolution in estimating the drug release profile by the dosage form. Gillespie and Veng-Pedersen (4) proposed the term "gastro-intestinal bioavailability" for the efficacy of drug release in the digestive tract.

The use of sustained or controlled release Lithium formulations in the treatment of manic depressive disorders has been suggested in order to reduce the plasma concentration peaks observed in steady state and which were due to relatively rapid absorption as compared to distribution (5-8).

In this paper the in vivo evaluation of a commercial preparation of sustained release lithium is described; the pharmacokinetic model used was based on the convolution of the polyexponential absorption-disposition function and a polynomial function for the gastro-intestinal release.

THEORETICAL MODEL AND DATA ANALYSIS

The theoretical model used to obtain the optimum profile of the response-time curve induced by administering a controlled release formulation and to evaluate the results is based on the convolution of the function which represents the gastro-intestinal

drug release process from the dosage form with that of the absorption-disposition of the drug in the organism. If the behaviour of the drug in the given response range is linear and retroalimentation phenomena are discounted, the curve corresponding to the response evoked by administering a drug dosage unit can be expressed by the equation:

$$D(t) = \sum_{n} a_i . e^{-\lambda_i . t} \qquad \text{Eq 1}$$

To interpret the gastro-intestinal release process we initially applied the customary scheme, i.e., considered part of the dose as released instantaneously (δ) and part as delayed by zero order kinetics with rate constant = bo and duration, θ:

$$I(t) = \begin{cases} \delta & , \quad t = 0 \\ bo & , \quad 0 < t \leq \theta \\ 0 & , \quad t > 0 \end{cases} \qquad \text{Eq 2}$$

The equation resulting from the convolution of Eq 1 and Eq 2 is for a single dose:

$$R(t) = \delta . \sum_{n} a_i . e^{-\lambda_i t} + bo . \sum_{n} \frac{a_i}{\lambda_i} (1 - e^{-\lambda_i t}) \qquad 0 \leq t \leq \theta$$

Eq 3

$$R(t) = \delta . \sum_{n} a_i . e^{-\lambda_i t} + bo . \sum_{n} \left[\frac{a_i}{\lambda_i} (1 - e^{-\lambda_i \theta}) . e^{-\lambda_i (t-\theta)} \right]$$

$$t \geq \theta$$

Eq 4

If one assumes repeated doses at regular intervals, τ, the result is at steady-state is:

$$R(t) = \delta \cdot \sum_{n} \frac{a_i \cdot e^{-\lambda_i t}}{1 - e^{-\lambda_i \tau}} + bo \cdot \sum_{n} \left[\frac{a_i}{\lambda_i} \cdot \frac{1 + (e^{-\lambda_i (\tau - \theta)} - 1) \cdot e^{-\lambda_i t}}{1 - e^{-\lambda_i \tau}} \right]$$

$$0 \leq t \leq \theta \leq \tau$$

Eq 5

$$R(t) = \delta \cdot \sum_{n} \frac{a_i \cdot e^{-\lambda_i t}}{1 - e^{-\lambda_i \tau}} + bo \cdot \sum_{n} \left[\frac{a_i}{\lambda_i} \cdot \frac{(e^{-\lambda_i (\tau - \theta)} - e^{-\lambda_i \tau}) \cdot e^{-\lambda_i t}}{1 - e^{-\lambda_i \tau}} \right]$$

$$t \geq \theta \leq \tau$$

Eq 6

To study the in vivo drug release process in the gastro-intestinal tract we used the Veng-Pedersen method (9) modified as follows: the input variable, gastro-intestinal release rate, was interpreted by an immediate release process where an amount of drug equal to δ was released plus a polynomial variable limited by the time interval $0 < t \leq \theta$

$$I(t) = \begin{cases} \delta, & t = 0 \\ \sum_{j=0}^{n} k_j \cdot t^j, & 0 < t < \theta \\ 0, & t > \theta \end{cases}$$

Eq 7

For m = 0, the release variable is equal to that given for the resolution of Equations 3-6. The result of the convolution of Equations 7 and 1 is:

$$R(t) = \delta . \sum_{n} a_i . e^{-\lambda_i t} + \sum_{m} b_j . \Omega_j(t)$$

Eq 8

where

$$\theta_j(t) = j! . \sum_{n} \frac{a_i}{-\lambda_i^{j+1}} . \left[e^{-\lambda_j t} - \sum_{k=0}^{j} \frac{(-\lambda_i . t)^k}{k!} \right] \quad 0 \leq t < \theta$$

Eq 9

$$\theta_j(t) = j! . \sum_{n} \frac{a_i}{-\lambda_i^{j+1}} \left[e^{-\lambda_i \theta} - \sum_{k=0}^{j} \frac{(-\lambda_i \theta)^k}{k!} \right] e^{-\lambda_i (t-\theta)}$$

$t > \theta$

Eq 10

The unknown factor added to the Veng-Pedersen method, θ, cannot be directly evaluated, and the release time must be arrived at by trial and error. Elsewhere we applied stepwise linear regression to estimate the vector b' = [∂, bo,...,bm].

The relative bioavailability of the controlled-release formulation compared with that of the instant-release formulation was statistically evaluated using the Bayesian method proposed by Mandallaz and Mau (10) which enabled us to calculate the a posteriori probability of the quotient, r, between a given parameter's experimentally-observed averages for two formulations (assessed by a crossover experimental design) being found within an acceptability interval [L1, L2].

The numerical deconvolution calculations utilized a program written for that purpose and multiple linear regression used the BMDP2R program (11). Student's t statistic was integrated by linear interpolation.

EXPERIMENTAL

Formulations Assayed. The sustained-release commercial preparation (Plenur, lot S-61) with a declared content of 400 mg Lithium carbonate, equivalent to 10.4 mM Li, complied with the requirements of the USP XXI Rev. (14) with regard to uniformity of weight and content. As reference, no 2 gelatine capsules of Lithium carbonate made up by ourselves were used.

Analytical Method. The Lithium samples were determined by atomic absorption spectrophotometry (Perkin Elmer Mod. 603) at 335.8 nm using an air-acetylene flame and three standards to calibrate each series of samples. The serum, urine and dissolution assay samples were diluted when appropiate with distilled, deionized water and assayed twice.

Dissolution Rate Tests. Apparatus I and Apparatus II as described in the USP XXI Rev. were used with a 6-vessel system (Turû-Grau Mod. D-6). All the assays were taken at 100 rpm, and distilled water, HCl 0.1 N and HCl 0.1 N + 0.1% polysorbate 80 were used as solvents.

Experimental Design. The crossover experimental design involved 10 healthy male and female volunteers (23 to 28 years of age weighing from 55 to 75 kg); the dose administered was 10.4 mM Lithium, equivalent to 1 tablet or two capsules. The washout period was 1 week. The dosage was administered with a standard Continental breakfast, no food being ingested for 6 hours thereafter. Urine samples were taken at 1 hourly intervals for the first six hours, at two-hourly intervals for the second 6 hours, and every twelve hours until 96 hours had elapsed. 3.5 hours after administration, a blood sample was taken to determine the renal Lithium clearance by the quotient between the renal excretion

TABLE 1

Values Obtained from the Urinary Excretion Curves, per Volunteer and Formulation According to Experimental Design.

	PERIOD I				PERIOD II		
SUB.	FORM.	Xmax	Vmax	tmax	FORM	Xmax	Vmax	tmax
A	COMP	11.4	0.750	11.0	CAP	10.4	1.08	2.5
B		9.73	0.478	7.0		9.74	0.823	1.5
H		3.71	0.149	5.5		10.1	0.861	1.5
I		3.17	0.155	5.5		8.12	0.610	0.5
J		9.75	0.480	7.0		10.6	0.986	2.5
C	CAP	10.5	1.18	3.5	COMP	7.86	0.348	7.0
D		9.92	0.653	3.5		9.10	0.343	7.0
E		9.98	0.652	1.5		7.39	0.281	2.5
F		10.6	1.16	1.5		9.17	0.410	4.5
G		10.7	1.28	1.5		10.3	0.548	7.0

SUB=Subject; FORM=Formulation; Xmax=Amount of Li excreted in the urine in the 96 h following administration; tmax=Midpoint of the time interval during which the maximum was observed; Vmax= maximum rate excretion observed at tmax.

measured in the 3rd-4th hour interval and the plasma concentration. The results of the study of the variance components of the Lithium clearance have already been reported (13); the mean value was 24.6 ml/min, similar to that given by other researchers for people with normal renal function (8).

RESULTS AND DISCUSSION

Table 1 set out, per volunteer and formulation, the values observed for the amounts of Lithium excreted in the urine in the 96 hours following administration (Xmax), the maximum values of the urine excretion curve [$(\Delta X/\Delta t)$max] and the midpoint of the time interval during which the maximum was observed (tmax). The mean values and typical deviations calculated for each

TABLE 2

Summarized Three-Way ANOVA Findings for Each Parameter together with the Mean Values and Standard Deviations Calculated. for Each Formulation.

Mean (±S.D.) CAP	PLEN	MS Error	Acceptability Interval	r	p
Xmax					
10.1 (2.73)	8.15 (0.76)	2.88	0.75 - 1.25	0.81	0.80
Xmax/ tmax					
0.928	0.394	0.0205	0.36 - 0.61	0.42	0.86
tmax					
2.0	6.4	N O T C O M P U T E D			

MS=Mean square of residual term from three-way ANOVA, with 8 degrees of freedom; r=Ratio mean tablets/mean capsules; p=probability, p(L1 ≤ r ≤ L2).

formulation together with other statistical parameters to be commented on later are given in Table 2.

Figure 1 shows the mean urinary excretion curves obtained for each formulation. The curve corresponding to the capsules was adjusted to a triexponential function by non-linear regression and the following equation for a 1 mM dose of Lithium was obtained:

$$dX/dt = 5.60 \cdot 10^{-3} \cdot e^{-0.490.t} + 0.330 \cdot 10^{-3} \cdot e^{-0.0397.t} - 5.93 \cdot 10^{-3} \cdot e^{-0.632.t}$$

Eq 11

The mean square of residuals was 0.00233; the adjustment was satisfactory, but the statistical parameters estimation was not, due in particular to the high negative correlation between the estimates for the coefficient and the exponent of the third exponential term.

By application of the numerical deconvolution method shown above, using the mean curves of each formulation, the variable

corresponding to the controlled-release tablets' gastro-intestinal release rate was estimated. The best adjustment was obtained by taking Θ = 8 h, to give:

$$I(0) = 1.0$$

$$I(t) = 0.941 - 2.39 \cdot 10^{-2} \cdot t, \quad 0 < t \leq \theta \qquad \text{Eq 12}$$

When this function was integrated, the equation for the accumulated amounts released *in vivo* was:

$$A(t) = 1.0 + 0.941 \cdot t - 1.20 \cdot 10^{-2} \cdot t^2 \qquad \text{Eq 13}$$

The curve generated by the result of the convolution of Equations 11 y 12 is given in Figure 1. From Equation 13, a first evaluation of the sustained-release tablets can be made; the gastro-intestinal release rate is always near to 0.94 mM/h, less than the 1.35 mM/h that it would take if the whole dose in the tablets were released at a uniform rate for 8 h.

Application of the numerical deconvolution method to the mean curves by-passes the problem of absorption-disposition pharmacokinetics parameters being constant between experiments carried out on the same subject. Biopharmaceutical evaluation invariably requires that the behaviour of the formulations be verified by *ad hoc* statistical methods which allow for variability in the subject. Moreover, most authors agree that the area under plasma level-time curve, the maximum of this curve and the maximum time, or its equivalent in the urinary excretion curve are the most suitable parameters for the evaluation of the bioavailability of sustained-release formulations. The problem resides in establishing the acceptability interval for each of the parameters when the controlled-release formulation is compared with a conventional formulation.

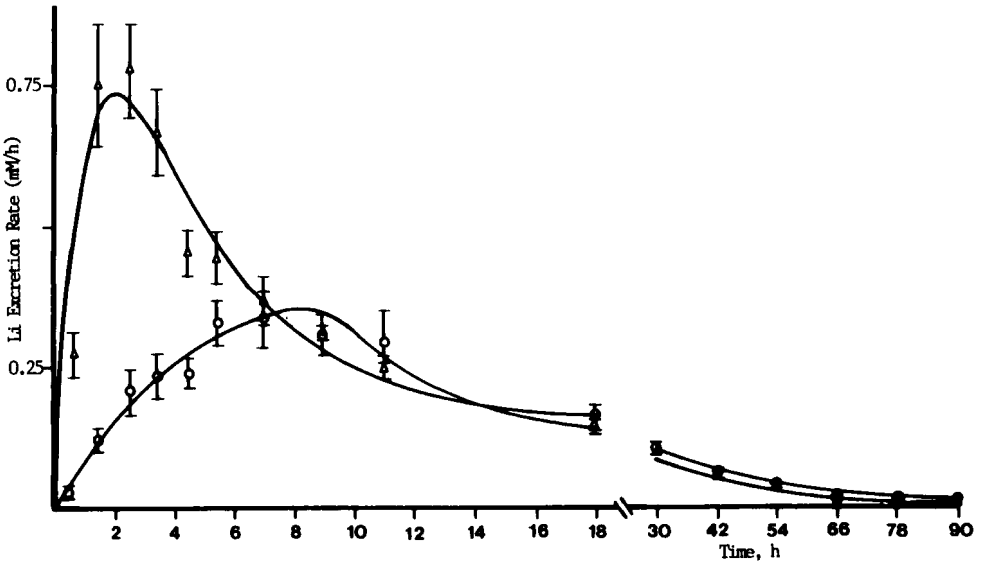

FIGURE 1
Mean and mean standard deviations of urinary excretion curves for capsules (Δ) ans sustained-release tablets (O). The drawn curves were obtained by non linear least squares regression, equal to 10.4 times Equation 11, and by numerical convolution of Equations 11 and 12, respectively.

For the parameter Xmax, 0.75 - 1.25 were chosen as the limits of acceptability for the quotient between the averages for the tablets and the capsules. To establish the limits of the other two parameters, the mean curves to be expected for a controlled release formulation were obtained by simulation, using Equations 3-6, the absorption disposition parameters estimated for the capsules (Equation 13) and various release kinetics (Figure 2). As as general rule, neither the manufacturers nor the published patents (14) provide information about the kinetics of the anticipated in vivo release and only very occasionally give details of the in vitro data obtained. We chose zero order kinetics as the reference process with a rate of 1.35 mM/h and 8 h

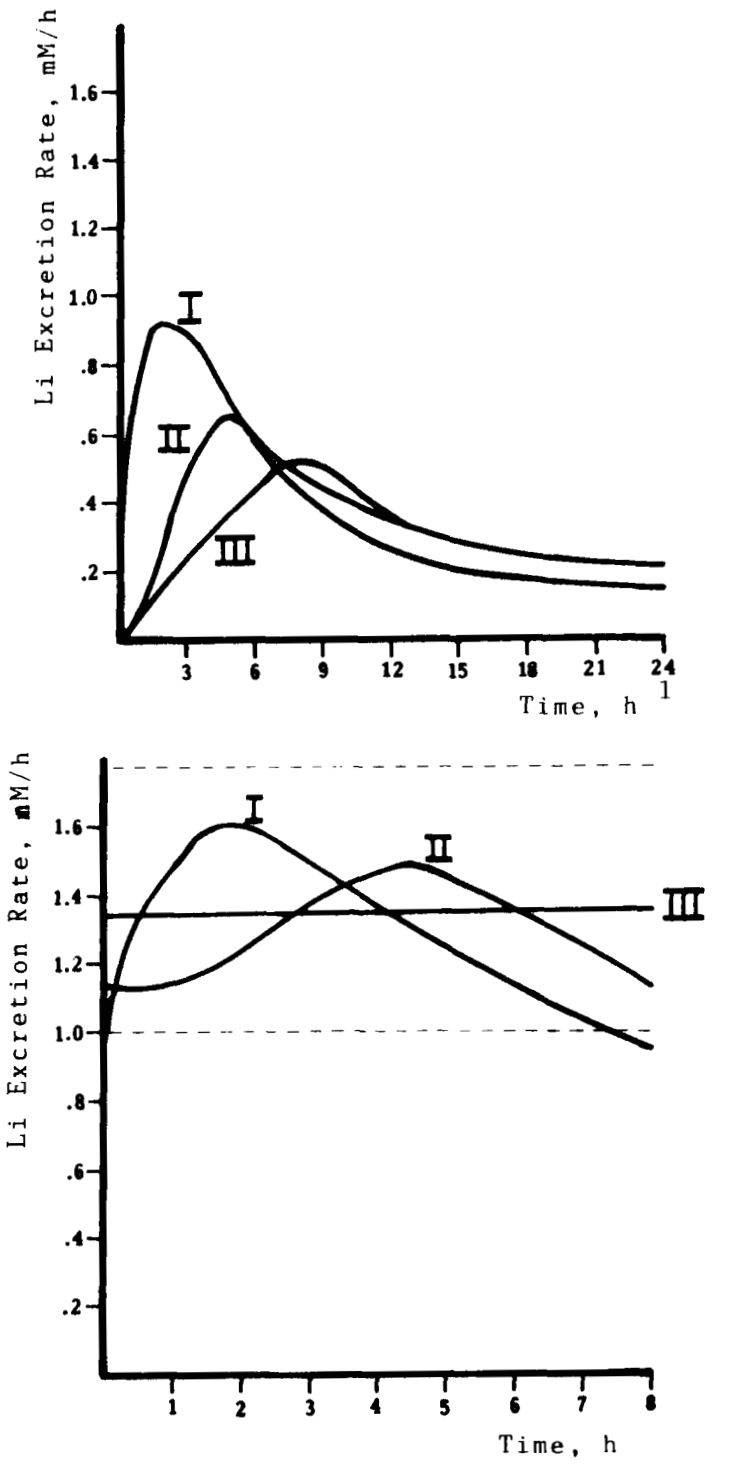

FIGURE 2

Theoretical urinary excretion curves obtained by simulation using Equation 3-4 for single dose (Left) and 5-6 for steady-state multiple doses (Right). The adsorption-disposition parameters used are those of Rquation 11. The release kinetics parameters were: CurveI, δ=10.4 mM; curve II, bo = 2.7 mM/h, θ = 4h; curve III, bo = 1.35 mM/h, θ =8h.

duration (curve III, Figure 2). The maximum value of this curve is very close to 60% of that observed for the capsules; if the absorbed fraction, 0.81, is also taken into account and an interval of ±25% is accepted, the acceptability limits of the quotient between the mean values calculated for the tablets and the capsules are 0.36 - 0.61. Due to the fact that the variable tmax was sampled discontinuously, we preferred not to analyse the data obtained for this parameter.

In Table 2 the three-way ANOVA findings for each parameter are summarized: the acceptability interval, the quotient between the averages calculated for the capsules and tablets and the probability that this is to be found within the acceptability limits. These findings bear witness to a reduction of the amount of Lithium absorbed; the null hypothesis of equal averages for the parameter Xmax was discounted with 0.05 to 0.01 probability. Furthermore, the quotient between the averages calculated for the ΔXmax/Δtmax parameter is 0.42, near to the midpoint of the corrected acceptability interval and the corresponding probability, 0.86, calculated *a posteriori.* Everything points to the release process being slow, taking the gastro-intestinal lithium reserve length (15) into consideration although this is not actually known. Our findings suggest that controlled- release Lithium formulations lasting more that 8 h cannot be devised without adversely affecting the absorbed dosage fraction.

In Figure 3(A) the mean dissolution curves found for the tablets taken on Apparatus I and Apparatus II of the USP XXI with distilled water, HCl 0.1 N, HCl 0.1 N + 0.1% polysorbate 80 as solvents are shown; the results obtained with the capsules are not included as the dissolution process was very quick and the data not applicable. When distilled water was used as solvent, the gel formed by hydratation of the tablets was trapped inside the rotating baskets of Apparatus I, while Apparatus II lent itself to gel dispersion and release of the Lithium. Clotting was reduced with the other two solvents, hence, the differences between the apparatuses is not so marked.

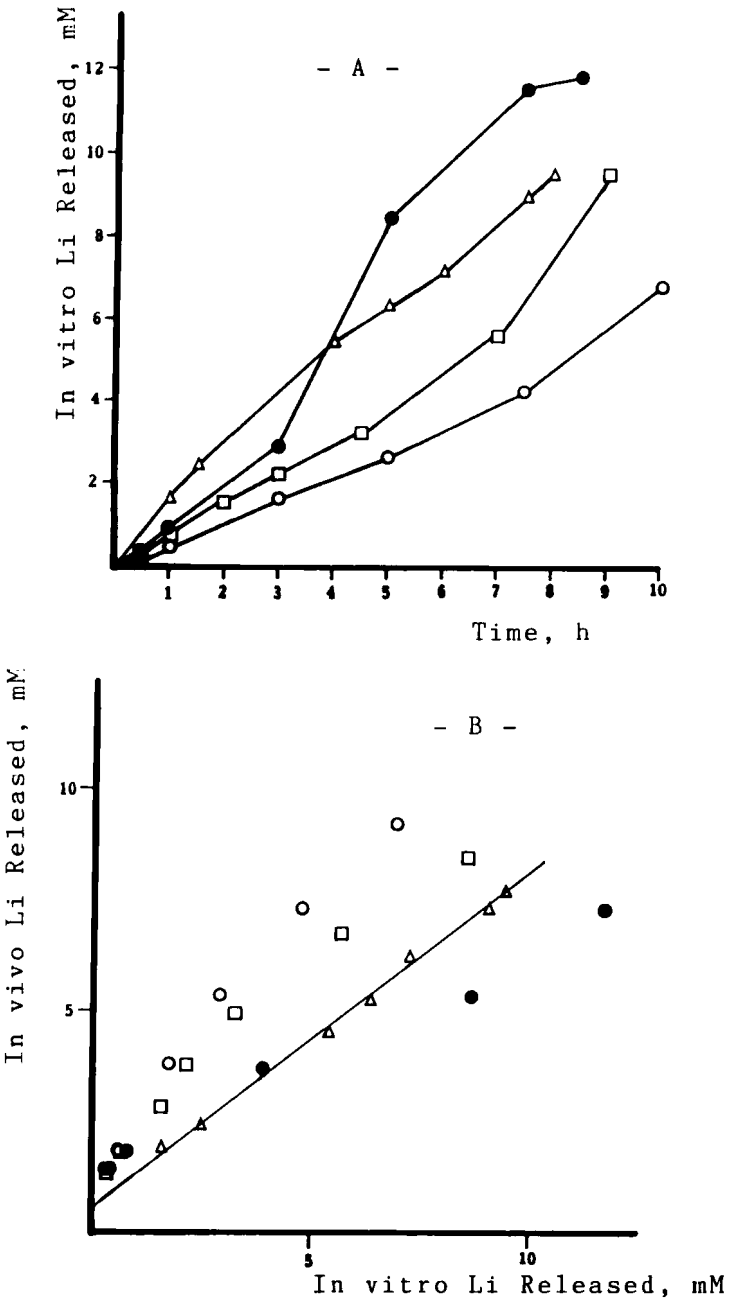

FIGURE 3
In vitro release curves (A) and in vivo-in vitro correlations (B).(0) Aparatus II and distilled water; () Apparatus I and distilled water; () Apparatus I and C1H 0.1 N + 0'1% polysorbate 80. In all cases, 900 ml of dissolution medium and 100 rpm.

Figure 3(B) shows the correlations observed between the mean amounts dissolved in vitro, or released in vivo calculated from Equation 13; as can be seen, the best results were obtained when Apparatus I and HCl 0.1 N were used. The parameters of the straight line regression are: bo = 0.588; b1 = 0.766; r = 0.9991.

To sum up, these results confirm that it is feasible to characterize the gastrointestinal release kinetics of drugs by pharmaceutical sustained release dosage forms, so important when designing, controlling and patenting these types of formulation; in addition, the problem of determining acceptability limits for one controlled release formulation compared with a conventional formulation have been solved, by bioequivalency assays, although the way in which the results obtained for the tmax should be treated has still to be evolved.

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