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THE IN VITRO AND IN VIVO PERFORMANCE OF A NOVEL SLOW RELEASE CAPSULE-COMPARED WITH A CONVENTIONAL CAPSULE

Narendra K.Jain* and Sharath U.Naik**
Pharmaceutics Laboratory, Pharmacy Department
Faculty of Technology and Engineering
M.S.University of Baroda
Baroda (INDIA) - 39001

ABSTRACT

A comparative in vitro and in vivo performance study of a novel slow release capsule (prepared using the new laser drilled controlled drug delivery system) and a conventional capsule dosage form has been made using tetracycline hydrochloride as a model drug. The influence of variation in drug delivery system design on the in vivo performance was studied by urinary excretion rate studies in human volunteers. Slow release capsules released its contents relatively slowly, over a period of time, both in vitro and in vivo, as compared to conventional capsules, with significantly similar K_e and $t_{\frac{1}{2}}$ values. Plasma C_{max} and t_{max} and AUC values were predicted based on the reported correlation between serum and urinary excretion data in single dose trials.

* Correspondence

** Present address: Concept Pharmaceuticals Pvt.Ltd.,
A 28/1, M.I.D.C.,
Chikalthana
Aurangabad. 431 210

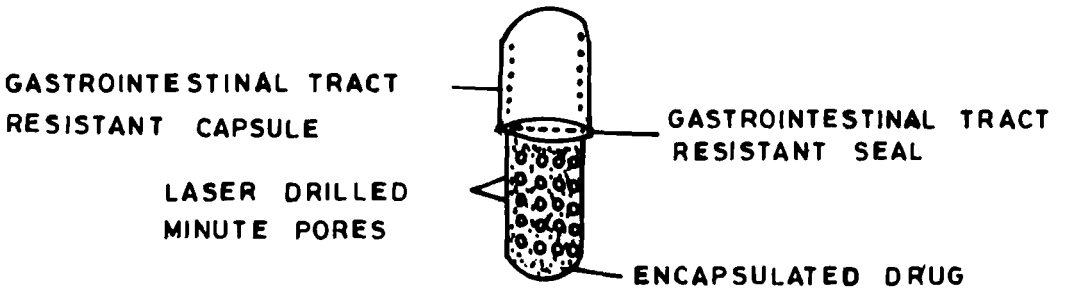

Figure.1
Schemetic representation of the new controlled release drug delivery system.

INTRODUCTION

A recent report indicated the use of laser drilling technique in designing a new controlled drug delivery system and its possible use in preparing a novel slow release capsule dosage form (1). The new drug delivery system (Fig.1) consists of a gastro intestinal tract resistant laser drilled hard genatin capsule with minute laser pores on the wall of the capsule, made using a CO_2 gas laser. Keeping the frequency constant at 1 pulse/s and varying the pulse-width of the laser between 100 and 420/ µs, minute laser drilled pores with average geomatric mean diameter ranging between 78.50 ± 1.57 and 25 ± 1.38/ µm respectively were obtained. These laser drilled pores can provide a controlled uninterrupted release of the encapsulated drug. The in vitro release of tetracycline hydrochloride from these capsules in 0.1 M Hcl, followed zero-order kinetics after an initial lag period of 30 min.

The total amount of unchanged tetracycline excreted in urine, in 48 to 72 h (Q_u^∞) provides an adequate means to evaluate preparations to establish correlations with in vitro dissolution rates and to study physiologic and pathologic conditions which affect the bioavailability of tetracycline (2). In order to effectively use the parameter Q_u^∞

urine collection must be made atleast 48 hours until most of the drug has been eliminated. The total amount of free drug appearing in the urine(Q_u^∞) can often, but not always be used to assess biological availability through the relationship shown in equation:

$$B_A = \frac{Q_{b(x)}}{Q_{b(S)}} = \frac{(K/K)\ Q^\infty_{u(x)}}{(K/K_e)\ Q^\infty_{u(s)}} = \frac{Q^\infty_{u(x)}}{Q^\infty_{u(s)} - 1} \qquad (1)$$

where, K_e is the first-order rate constant for elimination by renal excretion, $Q_{b(x)}$ and $Q_{b(s)}$ are the total amount of the drug absorbed from a test preparation (x) and a standard preparation(s) respectively. $Q^\infty_{(u)}$ and $Q^\infty_{u(s)}$ represent total amount of drug excreted in the urine of a test preparation and a standard preparation respectively. The assessment of biologic availability by the ratios of Q_u^∞ (as shown in equation (1) is dependent on the assumption of constancy of K_e/K which equivalent to the fraction of the drug reaching the circulation, which is excreted unchanged in urine (4).

The objectives of the present investigation were to:

i) use the new drug delivery system in preparing a novel slow release capsule dosage form, using tetracycline hydrochloride as a model drug;

and

ii) make a comparative in vitro and in vivo performance evaluation of slow release and conventional capsule dosage forms.

MATERIALS

Tetracycline hydrochloride (Synbiotics, Wadi Wadi, Baroda, India) dioctyl sodium sulfosussinate (Doxinate, Hoechst, Aktiegese) Schalft, Badvibel, Germany), uranium acetate (B.D.H.England) and β-thio propionic acid (Thiolactic acid, Fluka AG., Chem. Fabrik CH.9470, Buchs). All the above materials were used as received.

METHODS

Novel Slow Release and Conventional Tetracycline Capsules

Novel slow release tetracycline capsules (slow release capsules) were prepared by encapsulating 250 mg of tetracycline hydrochloride, coated with 0.5% w/w dioctyl sodium sulfosuccinate in gastrointestinal tract resistant laser drilled capsules. The capsules contained 100 minutes laser drilled pores; with an average geometric mean diameter equal to 100 ± 1.41/ μm, providing a total surface area of about 3.38 cm^2/capsule for the release of the encapsulated drug. A mixture of lactose and sucrose in an optimised proportion was used as the diluent and the capsules were band sealed with a gastro-intestinal tract resistant material.

The conventional hard gelatin tetracycline capsules (conventional capsules) were prepared by encapsulating the same contents as used for the preparation of slow release capsules in conventional hard gelatin capsules.

In Vitro Evaluation

Dissolution studies were carried out using a basket stirrer assembly of USP XX (5) dissolution apparatus, at a stirrer speed of 100 rpm, with dissolution media temperature held at 37 ± 0.5°C. 300.0ml each of 1.2, 2.5, 4.5, 7.0 and 7.5 pH dissolution media were prepared and changed at different intervals of time as per the method recommended in NF XIV (6), under timed release tablets and capsules in vitro test procedure. 5.0 ml samples were withdrawn at the end of 0.1, 1.0, 2.0, 3.5, 5.0, 7.0 and 8.0 h time intervals, filtered and analysed at 353 mm using a spectrophotometer.[1]

1. Model VSU 2-P, C.Z. Spectrophotometer, Germany.

In Vivo Studies

A crossover study was carried out with one week washout period in between on four healthy human volunteers, weighing between 55 and 70 kg, 26-34 years old, as the subjects. The treatment consisted of slow release capsules (Treatment.I) and conventional capsules Treatment.II). The subjects were advised fasting 3 h before and 3 h after receiving each of the treatments. Capsules were administered orally with 200 ml of water. Urine samples were collected predose and at 1,2,4,6,8,10,12,14,18,24,30,36,42 and 48 h post administration. Sujects were advised to take about 100 ml of water every hour, in the initial 8 h after capsule administration. The urine volumes were measured and recorded after each collection and aliquots were frozen until assayed.

Spectrophotocolorimetric Determination of Tetracycline in Urine.

The analytical procedure used for the determination of the total amount of unchanged tetracycline excreted in urine involves spectrophotocolorimetric measurements of the colour of uranium-tetracycline complex (7), produced by heating pretreated urine samples (8) (prepared as described below) containing about 5 to 30/ µg of tetracycline with 0.2 ml of 0.1% (w/v) uranyl acetate solution in 1:1 mixture of dioxan:water, at 420 nm.

The urine sample was prepared by heating 1.0 ml of aliquot with 1.0 ml of dioxan, 2.0 ml of 0.1 N HCL and 0.5 ml of 0.1% (w/v) solution of β-thio propionic acid in a water bath for 30 min. (polyethylene balls over the top of each tube were used to minimise loss by evaporation during heating). The tubes were then cooled to room temperature before the addition of uranyl acetage solution.

RESULTS AND DISCUSSION

The dissolution profile of the two capsules studied as shown in Fig.2 was constructed by plotting percentage drug dissolved versus

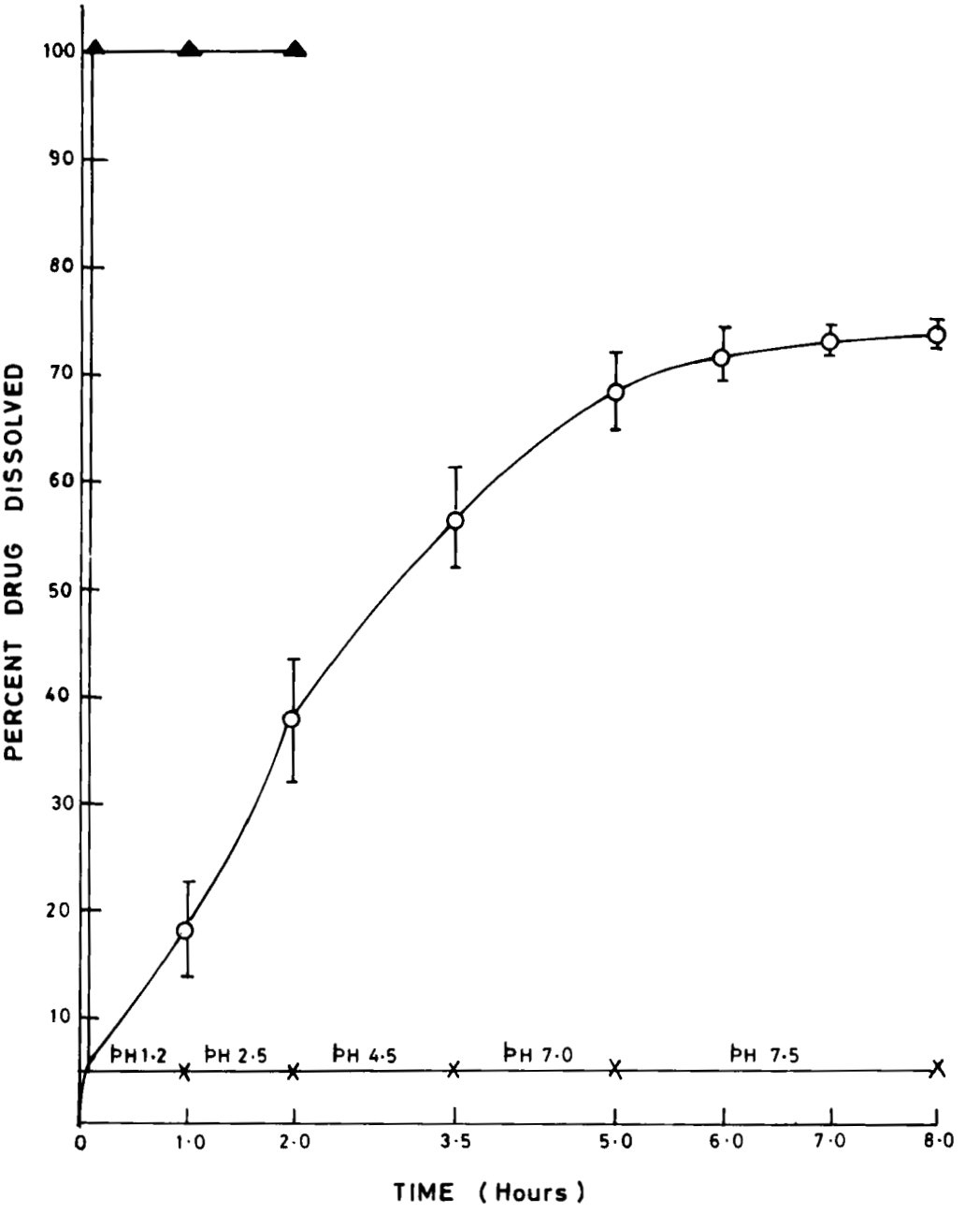

Figure.2

Percentage tetracycline hydrochloride dissolved as a function of time from the two capsules.

Key: 0 Slow release capsule, and

▲ Conventional Capsule. n = 6, mean ± SD

time. The profile indicates that the slow release capaule releases about 74.4% of the drug slowly, at different rates under different pH conditions over a period of 8 h and the time required for the capsule to release 50% of the contents ($T_{50\%}$) was 2.85 h. The slow release capsule showed highest dissolution rate at pH 2.5 and 4.5 followed by pH 1.2 and 7.0 while the rate was very slow in the alkaline pH 7.5. Unlike the slow release capsules, the conventional capsules showed a rapid dissolution rate at pH 1.2 with T_{50}% value less than 0.1 h.

Fig.3 shows a semilogarithmic plot of the average unmetabolized drug remaining to be excreted $X_u^\infty - X_u$ versus time, t, drawn based on sigma - minus method (9). The scattered points in the plot (Fig.3) were linearised by least-square fit method (10). The best fit was obtained by the logarithmic transformation of $X_u^\infty - X_u$ versus time data as shown in Table.I. The calculated values corresponding to Treatment.I and II equal to 0.036 and 0.038 mg h-1 respectively, represented the slope of corresponding linear curves in Fig.3. Hence the elimination rate constant of tetracycline, $K_e = 2.303\alpha$ and elimination half-life $t_{\frac{1}{2}} = \frac{0.693}{ke}$ corresponding to Treatment.I and II were calculated. No significant difference ($P > 0.01$) in the values of $t_{\frac{1}{2}}$ 8.4 h and K_e 0.083 $mg.h^{-1}$ were obtained with Treatment.I as compared to the values of $t_{\frac{1}{2}}$, 7, 9 h and K_e 0.088 mg h^{-1} obtained with Treatment.II. These findings were well in agreement with reported (2) $t_{\frac{1}{2}}$ 9.4 h and K_e 0.074 mg h^{-1} values obtained after oral administration of 250.0 mg capsules of tetracycline hydrochloride. The cumulative amount of tetracycline excreted unchanged. X_u^∞ equal to 55.53 mg and 68.13 mg corresponding to Treatment.I and II respectively are in good agreement with reported (11) value equal to 92.0 mg and 71.0 mg obtained after oral administration of 250.0 mg of oral dose of aqueous solution of the drug under fasting and after breakfast conditions respectively in human subjects.

Table.II illustrates the comparison of urinary excretion data, at the midpoint of each urine collection time, obtained with Treatment

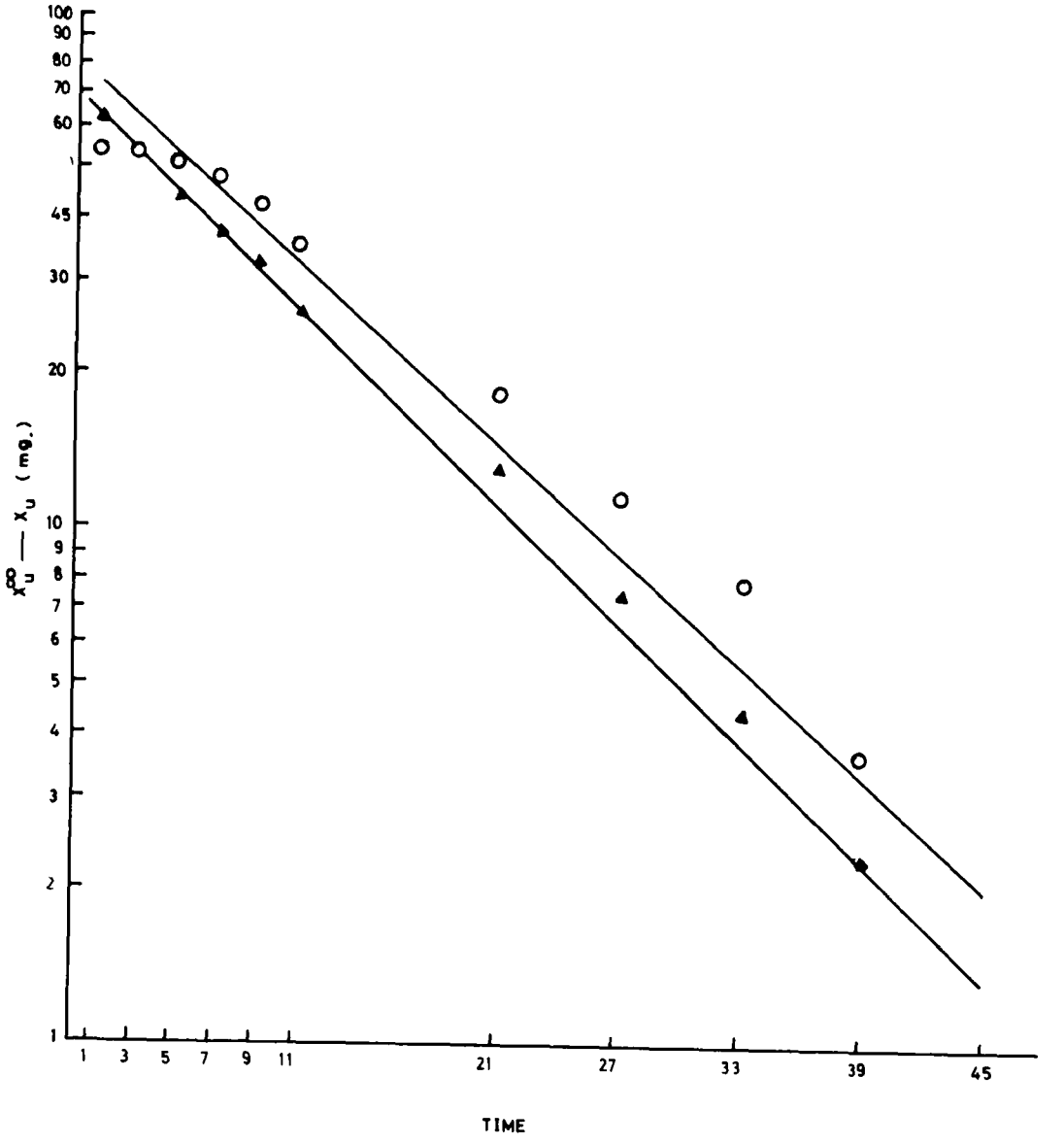

Figure.3

Semilogarithmic plot of the amount of unchanged tetracycline remaining to be excreted ($X^{\infty}_u - x_u$) versus time (t) for the two treatments studied. Key: ○ Treatment.I and ▲, Treatment.II. n = 4, mean

TABLE.I: Logarithmic Transformation of the amount of Unchanged Drug Remaining to Excreted Versus Time for data for the Two Treatments Studied, by Least - Square - Fit Method.

Sl. No.	X Time in Hrs.	Logarithmic Transformation of $X_u^\infty - X_u = Y$											
		Treatment.I (Slow release capsules)						Treatment.II (Conventional Capsules)					
		X_u	$X_u^\infty - X_u = Y$	Log Y	$Z = \alpha X + \beta$	$\tilde{Y}$ a	Δ^{2b}	X_u	$X_u^\infty - X_u = Y$	Log Y	$Z = \alpha X + \beta$	$\tilde{Y}$ a	Δ^{2b}
1.	1.0	0.55	54.98	1.7402	1.8742	74.85	394.82	5.23	62.9	1.7987	1.8157	65.42	4.93
2.	3.0	1.89	53.64	1.7295	1.8022	63.65	95.65	16.75	51.38	1.7108	1.7397	54.92	12.53
3.	5.0	4.34	51.19	1.7092	1.7302	53.73	6.45	23.68	44.45	1.6479	1.6637	46.10	2.72
4.	7.0	7.44	48.09	1.6820	1.6582	45.52	6.61	30.93	37.20	1.5705	1.5877	38.70	2.25
5.	9.0	13.40	42.13	1.6246	1.5862	38.56	12.75	35.67	32.46	1.5113	1.5117	32.48	0.004
6.	11.0	20.31	35.22	1.5467	1.5142	32.67	6.50	30.24	27.89	1.4454	1.4357	27.23	0.436
7.	21.0	37.08	18.45	1.2659	1.1542	14.27	17.47	54.80	13.33	1.1249	1.0577	11.37	3.840
8.	27.0	43.58	11.95	1.0763	0.9382	8.67	10.76	60.60	7.53	0.8768	0.8277	6.73	0.650
9.	33.0	48.42	7.11	0.8519	0.7222	5.27	3.39	63.66	4.47	0.6503	0.5997	3.96	0.260
10.	39.0	51.98	3.55	0.5502	0.5062	3.21	0.12	65.62	2.61	0.4166	0.3717	2.35	0.066
11.	45.0	55.53	-	-	0.2902	1.95	-	68.13	-	-	0.1437	1.39	-

a = $\tilde{Y}$ value corresponding to Z, $\tilde{Y} - (Y - \alpha X - \beta)$; b, $\Delta = \tilde{Y} - Y$

TABLE.II.

Mean Urinary Excretion Rate compared by paired t-test at the Mid-point of each urine collection time.

No.	Time (h)	Urinary Excretion Rate (mean ± SE) Treatment.I[b]	Treatment.II[c]	Calculated t-value	Significance level by paired t-test
1.	1.0	0.28 ± 0.08	3.14 ± 0.39	14.30	0.01
2.	3.0	0.67 ± 0.26	5.76 ± 0.87	6.28	0.01
3.	5.0	1.23 ± 0.31	3.47 ± 0.46	2.23	NS[a]
4.	7.0	1.55 ± 0.21	3.63 ± 0.57	3.50	NS
5.	9.0	2.98 ± 0.21	2.37 ± 0.43	2.01	NS
6.	11.0	3.46 ± 0.2	2.29 ± 0.47	2.71	NS
7.	21.0	1.25 ± 1.1	1.05 ± 0.61	1.68	NS
8.	27.0	1.08 ± 0.8	0.97 ± 0.56	2.44	NS
9.	33.0	0.81 ± 0.37	0.50 ± 0.08	2.44	NS
10.	39.0	0.59 ± 0.27	0.32 ± 0.16	3.17	NS
11.	45.0	0.59 ± 0.29	0.43 ± 0.05	4.15	NS

a = Not Significant ($P > 0.001$)
b = Slow release capsules
c = Conventional Capsules

I and II, by paired t-test. The mean excretion rate of Treatment.II as compared to Treatment.I remained significantly higher ($P < 0.01$) only in the initial 3 h and then the rate though was higher, was statistically not significant. The significantly low excretion rate in the initial hours in the case of slow release capsule may be attributed to relatively slow release of the encapsulated drug from the capsule over a period of time at different transit points in the GIT unlike conventional capsule which must have released the drug immediately after administration, in the stomach as apparent from the in vitro dissolution results (Fig.2).

Approximate serum level concentrations of tetracycline at different intervals of time as shown in Fig.4 were predicted based on the reported (2) correlation between urinary excretion rates and serum concentrations of tetracycline (determined) at the mid-point of each urine collection time). The predicted values of t_{max} 11.0h and C_{max} 0.067 ± 0.2/ µg. ml^{-1} for treatment.I were considerably different from predicted t_{max} 3 h and C_{max} 1.10 ± 0.20 / $\mu g.ml^{-1}$ values of Treatment.II. The predicted t_{max} and C_{max} values of tetracycline obtained with conventional capsule correlated well with the reported t_{max} value, 2.5 h (12) and C_{max} value, 1.33 $\mu g ml^{-1}$(13) obtained after oral administration of tetracycline hydrochloride. The relative absorption of tetracycline from Treatment.I with respect to Treatment. II. ie., the ratio of AUC $_{0-48}$ determined by Trapezoidal rule method (14)for Treatment.I and II respectively was found to be equal to 0.84.

The correlation between serum and urinary excretion data (2) was based on the assumption of constancy of K_e /K which is equivalent to the fraction of the drug reaching circulation which is excreted unchanged in urine. The validation of this assumption with respect to the present study was made by plotting urinary excretion rate versus serum concentration and cumulative amount of unchanged tetracycline excreted after 48 h versus AUC (Fig.5) based on the Equations

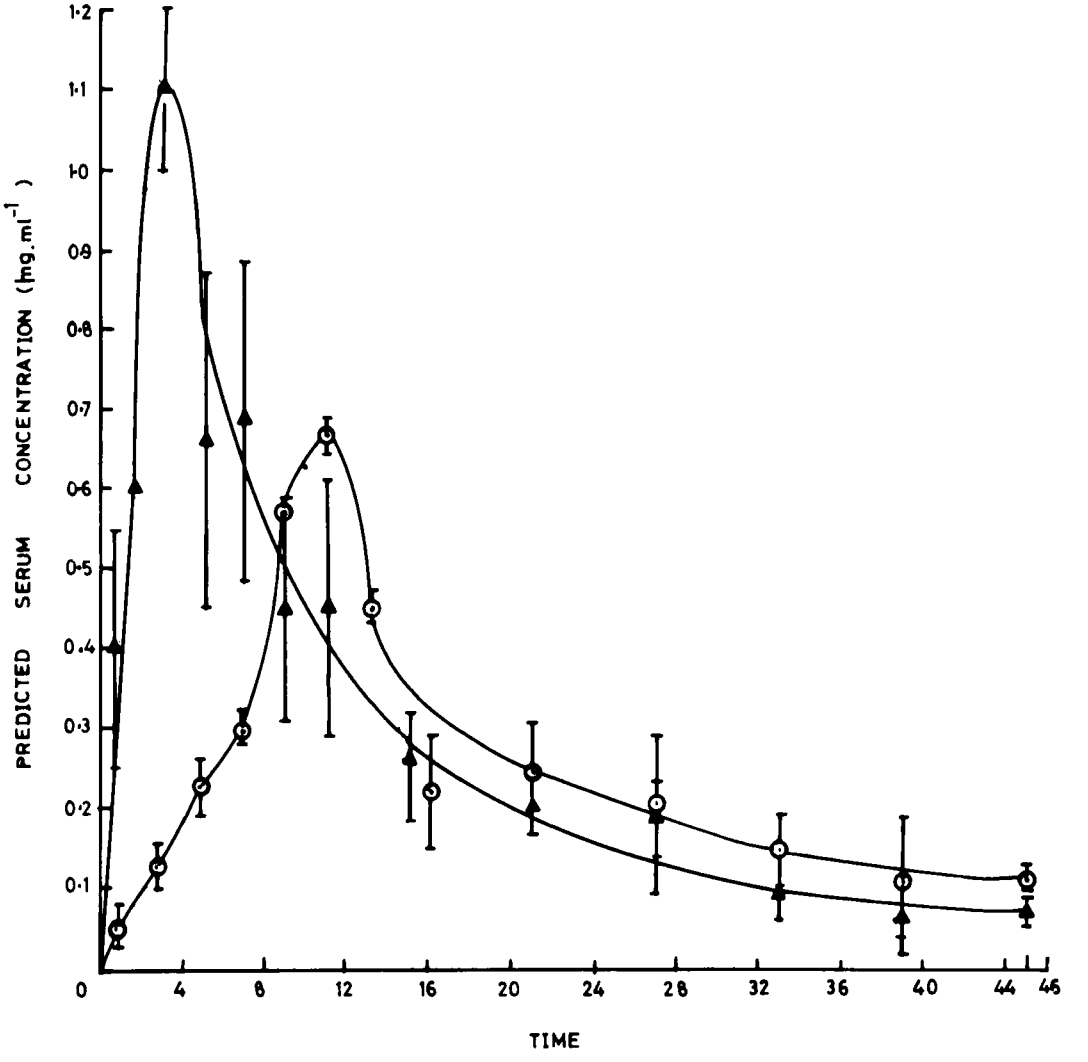

Figure.4

Predicted serum level concentration as a function of time for the two treatments studied.

Key: O Treatment.I and ▲, Treatment.II.

2 and 3 respectively, where, cl_r is the renal clearance of the drug,

$$\frac{\frac{\Delta Q}{\Delta t}}{C_{st}} = cl_r \qquad \text{.....(2)}$$

$$\frac{Qu}{AUC} = \frac{(K_e/K)\, Q_b}{} \bullet K_e\, V_d = cl_r \qquad \text{.....(3)}$$

$\frac{\Delta Q}{\Delta t}$ is the mean urinary excretion rate and C_{st} is the serum concentration at the mean time of the urine collection period. The slopes of the plots shown in Fig.5, equal to average clearance of 88.9 ml min^{-1} and 84.34 ml min^{-1} were in good agreement with the values 88.1 ml min and 80.1 ml min^{-1} respectively, obtained by Barr et al. (2) by the same method. No significant difference between the slope values corresponding to Treatment.I and II were observed indicating that (i) the assumption made by Barr et al to correlate serum and urinary excretion data is true for the present study also and (ii) the modification in the drug delivery system design, of the kind made in the present study do not affect K_e and V_d.

The observed considerably high C_{max} and t_{max} values, insignificant difference in $t_{\frac{1}{2}}$ and K_e values and relative absorption of 84.0% of treatment I as compared to Treatment II indicate that slow release capsule must have released the drug contents relatively slowly, over a period of time at different transit sites in the gastrointestinal tract, thus avoiding dose dumping in the stomach. The slow release capsule could also maintain reasonably high blood levels for a longer duration of time giving more time for the drug in the blood to interact with the active sites without much loss of bioavailability. The possible advantages of such slow release capsule, therefore, could be:

I. the potential hazard associated with encapsulation of highly soluble drug in conventional hard gelatin capsule due to sudden release of the contents resulting in localized high concentrations of the drug (15) could be overcome;

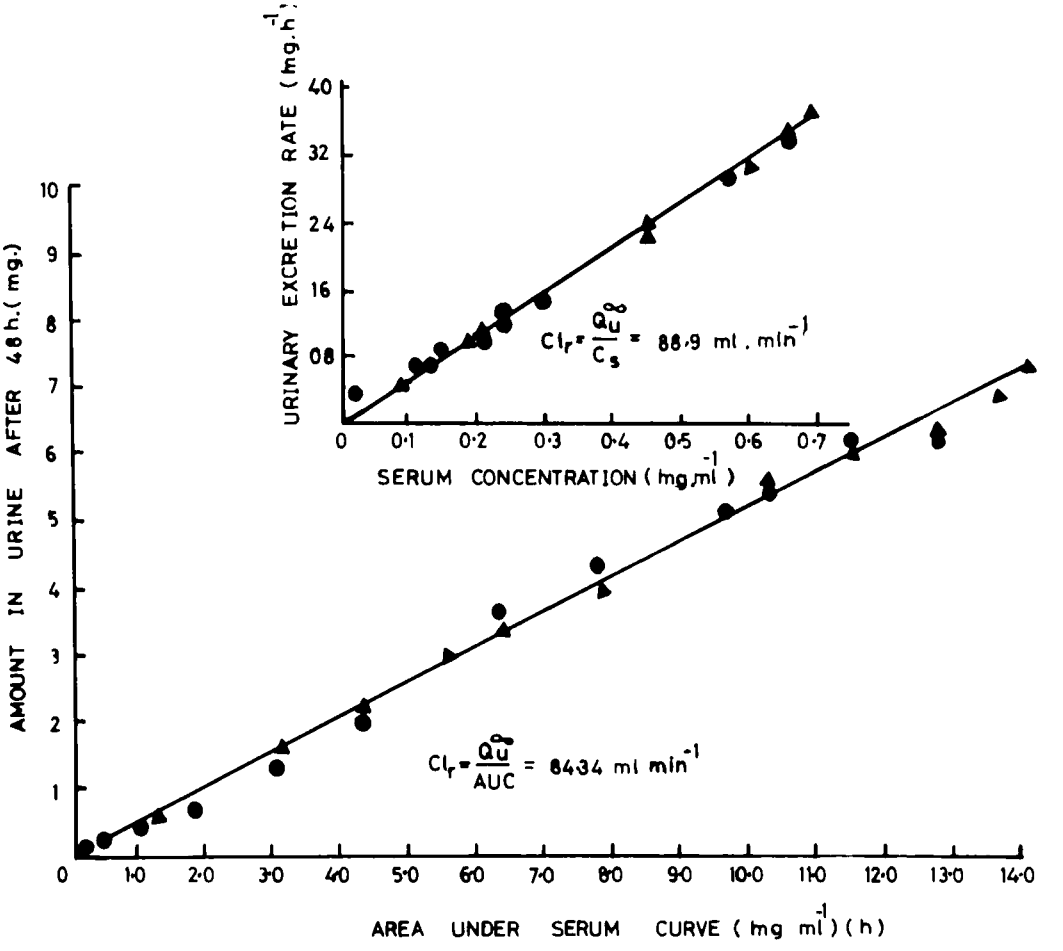

Figure.5

Relationship between urinary excretion rates of tetracycline and serum concentrations and cumulative amount of tetracycline excreted after 48 h and the total area under the predicted tetracycline concentrations in serum versus time curve determined at mid-point of each urine collection interval after oral administration of a 250 mg dose in the two dosage forms, studied.

Key: 0 Slow release capsule, and ,

▲ Conventional capsule. n = 4 mean

II. the drug with narrow therapeutic range could be administered by oral route more safely because of relatively low C_{max} obtained; and

III. the therapeutic efficacy of the drug may be increased and the frequency of administration may be reduced. Since slow release capsule maintains considerably high blood levels for a longer duration of time, thus allowing longer and better interaction of the drug at the active sites.

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