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DEVELOPMENT OF A NEW CONTROLLED RELEASE THEOPHYLLINE TABLET: IN VITRO AND IN VIVO STUDIES

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ABSTRACT

Five formulations of controlled release theophylline tablets, specially shaped to a multi scored approximately rectangular structure, manually dividable accurately and conveniently into bisectional or trisectional subdosage units were prepared, using ethyl cellulose/hydroxypropylcellulose and Eudragit RL. The influence of two parameters (fillers, granulation) on the dissolution rate of all tablets was studied. It was found that granulation yields greater retardation in dissolution rate, in comparison to direct compression. No significant differences were found among the fillers used, concerning the dissolution rate.

* Correspondence

A comparison of profiles from Theodur® in water media to those of theophylline tablets of formulation I, showed a remarkable similarity concerning the release of theophylline. Thus, there was a further bioavailability study of this formulation. A graph of plasma theophylline concentration versus time was prepared. Area under curve extrapolated to infinity was determinated with a standard mathematical method and a predicted steady-state blood serum theophylline concentration was estimated.

INTRODUCTION

In recent years, considerable attention has been focused on the development of the formulations that will release drug at a controlled rate of a prolinged period of time. As carriers for this purpose there have been used cellulose and its derivatives[1], waxes[2], polysaccharides[3], acrylic resins[4], mastix[5]. Depending on the nature of the carrier, drug release can be more or less retarded.

Theophylline therapy of airways obstruction associated with asthma and chronic broncitis with conventional immediate release regiments -tablets or solutions- requires treatment every six hours, due to theophylline's short half life, which often effects patient compliance. The half life of theophylline in the blood serum varies considerably from patient to patient and is altered by several conditions like smoking, viral infection, heart failure etc. Children are also rapid theophilline metabolizers.

Therefore the development of a sustained-release tablet, that could permit dosage at 12-hour intervals (twice a day scedule) with an at least 90% theophylline absorption and maintenance of a blood serum theophylline concentration within normal therapeutic least toxic risk range of 8 to 20 µg/ml would solve a significant problem.

The present investigation is concerned with the evaluation of three possible carriers for the preparation of controlled release theophylline tablets (ethylcellulose/

hydroxypropylcellulose, Eudragit RL), as well as of the influence of some fillers (mannitol, sorbit, dextrose) on the dissolution rate. In the case of cellulose, the influence of granulation, was also studied. In the case of theophylline we are further interested in the capability of dividing a dividable tablet into individual doses. This means that the patient will be able to bisect and trisect the tablet and take by himself the 1/2, 1/3 or 2/3 of the tablet. For this purpose a rectangle dividose(TM) tablet was prepared[6]. The test concerning the drug release rate from a rectangular and a usual (normal) tablet at the same content showed that there are no differences. A further study was made to compare the dissolution properties of formulation I to those of a commercially available controlled release theophylline tablet (Theodur®).

The unique dividose configuration of the tablet pro - vides for therapeutic effect within the range of 5 to 10 µg/ml of serum theophylline in case where individualization of dosage is required.

EXPERIMENTAL

In vitro

Materials*

The materials used in this study were: Theophylline anhydrous (powder, Ph. Eur.), cellulose (Avicel PH 101-FMC Co), ethyl cellulose pure (Dow Chemical Co), Hydroxypropylcellulose (Hercules Inc. USA), Eudragit RL (Röhm Pharma GmbH), mannitol (USP XXI), dextrose (USP XXI), sorbit instant (Merck).

Preparation of tablets

Five tablet formulations were prepared, each containing 300 mg of theophylline. Tablets were pressed on a Korsch tabletting machine, using a rectangular(TM) punch and die*.

* Courtesy of Bristol Hellas S.A., Athens.

Formulation I

Theophylline and cellulose were mixed and then granulated with a water solution of hydroxypropylcellylose, to prepare granules of 0.8-0.9 mm size. Granules were dried for over 24 hours, at 55°C. Granulometric analysis showed 19% fines (<100 microns). Finally, granules were pressed to give tablets of 320 mg of weight and a hardness of 20 Kp.

Formulation II

Theophylline was mixed for five min. in a Turbula mixer with ethyl cellulose. The mixture was pressed in tablets of 349 mg weight and 20 Kp hardness.

Formulation III

Theophylline and Eudragit RL were mixed for 10 min. in a Turbula mixer. Then mannitol was added and the new mixture was mixed for 5 more minutes. The mixture was pressed in tablets of 484 mg of weight and 20 Kp hardness.

Formulation IV

As in formulation III, using dextrose instead of mannitol. Tablet weight 500 mg, hardness 20 Kp.

Formulation V

As in formulation III, using sorbit instead of mannitol. Tablet weight 500 mg, hardness 20 Kp.

Quality tests

Tablets were tested for water content, weight variation, content uniformity, hardness (pfizer hardness tester) and dissolution rate. The dissolution rate test was applied according to the USP XX^{7} Paddle medthod using 900 ml of water at 37 ± 0.1°C and a rotating paddle at 50 rpm.

Content uniformity test

It was run for all formulations except formulation III. Each tablet was dissolved in water in a 1000 ml volumetric flask. Samples of 5 ml each were taken and diluted up to100 ml. The concentration in theophylline of the last solution was measured spectrophotometrically at maximum absorbance

at 268 nm. A standard curve was used for the calculation. The accuracy of this method was 3%.

Dissolution test

Samples of 5 ml each were taken at time intervals of ½, 1, 2, 3, 4, 5 and 8 hours. Each sample was diluted in a volumetric flask up to 50 ml. The absorption of the solutions was read at maximum 268 nm. Concentrations were calculated on the basis of a standard curve.

In vivo

The rate and degree of absorption of theophylline and the steady-state serum theophylline levels achieved after a single dose administration were determined on 12 non smoking volunteers. The volunteers, aged 24 to 60 yrs, were selected to participate according to a medical protocole and after clinical examination. No xanthine containing foods (coffee, tea, cola beverages etc.) erte taken by the volunteers for 24 hours prior to the test day.

Each participant received one tablet with 100 ml of water. Blood samples of sufficient volume to deliver 5 ml of plasma were drawm immediately prior to drug administration and at 1/4, 1/2, 1, 2, 3, 4, 6, 8, 12 16 and 24 hours thereafter. Serum samples obtained from each blood sample were kept refrigerated and later analysed by simple sensitive and specific high pressure liquid chromatographic method[8]. The method was chosen for its specifity and sensitivity of a number of available methods for the analysis of theophylline in biological liquids using ultraviolet spectrophotometry[9], GLC[10] and HPLC[11, 12, 13].

Materials and chromatographic parameters

A high pressure liguid chromatography with fixed wavelength (280 nm) UV detector was used. The mobile phase contained 1% distilled water, 5% methanol (USP) and 25% 2-butanol in n-hexane (HPLC grade). Theophylline reference standard and caffeine (FERAK BERLIN) were used as obtained. The mobile phase was pumped at 3.3 ml/min through a hifh efficiency stainless steel column (μ porasil, Waters Asso-

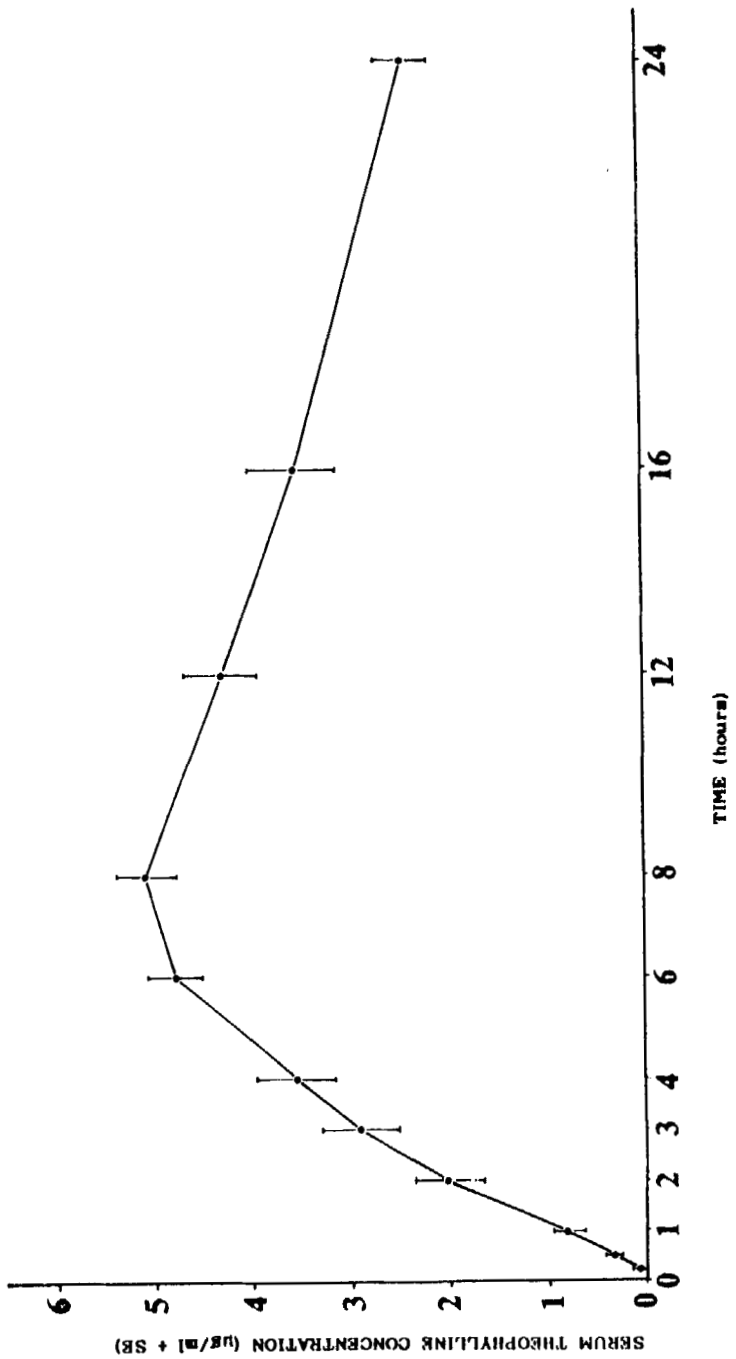

Fig. 1. Mean (± SEM) Serum theophylline concentration versus time curve for twelve volunteers who ingested a 300 mg sustained-release tablet.

ciates PN 27477). A 100 ml loop was used for injections of constant volume of the extraction solution. Theophylline retention time was 2.7 min and coffeine retention time was 5.1 min, comparable to that reported in the literature[8]. A standard curve of theophylline was used for the calculations. The correlation coefficient of this curve was 0.9997.

Pharmacokinetic Data Analysis. Theophylline concentration versus time curve from a single dose 300 mg sustained release tablet is shown in figure 1. The mean pharmacokinetic parameters are listed in table I. The methodology used for the calculation of their values is presented below.

First order elimination rate constant (K_{el}) was calculated from the terminal portion of this curve (the log of the last four points of serum theophylline concentration was plotted vs. time; R = 0.9995):

$$\log C = \log C_o - (K_{el} \cdot t/2.303)$$

where C is the serum theophylline concentration at any time t and C_o is the extrapolated serum theophylline concentration at zero time, i.e., the y-intercept.

Elimination half-life value ($t_{\frac{1}{2}}$) was calculated by:

$$t_{\frac{1}{2}} = 0.693/K_{el}$$

Area under the serum theophylline concentration versus time curve (AUCo-∞) and the lag time were calculated

Table I. Mean pharmacokinetic parameters

1. K_{el} = 0.047 hrs^{-1}	7. lag time = 0.27 hr
2. $t_{\frac{1}{2}}$ = 14.7 hrs	8. C_{ss} = 11.2 µg/mL
3. T_{max} = 7.42±2.1 hrs	9. F = 0.84
4. C_{max} = 5.34±1.06 µg/mL	10. Cl = 1.88 L/hr
5. AUCo→∞ = 134.0mg hr/L	11. Fluctuation = 23%
6. V_D = 40.0 L	

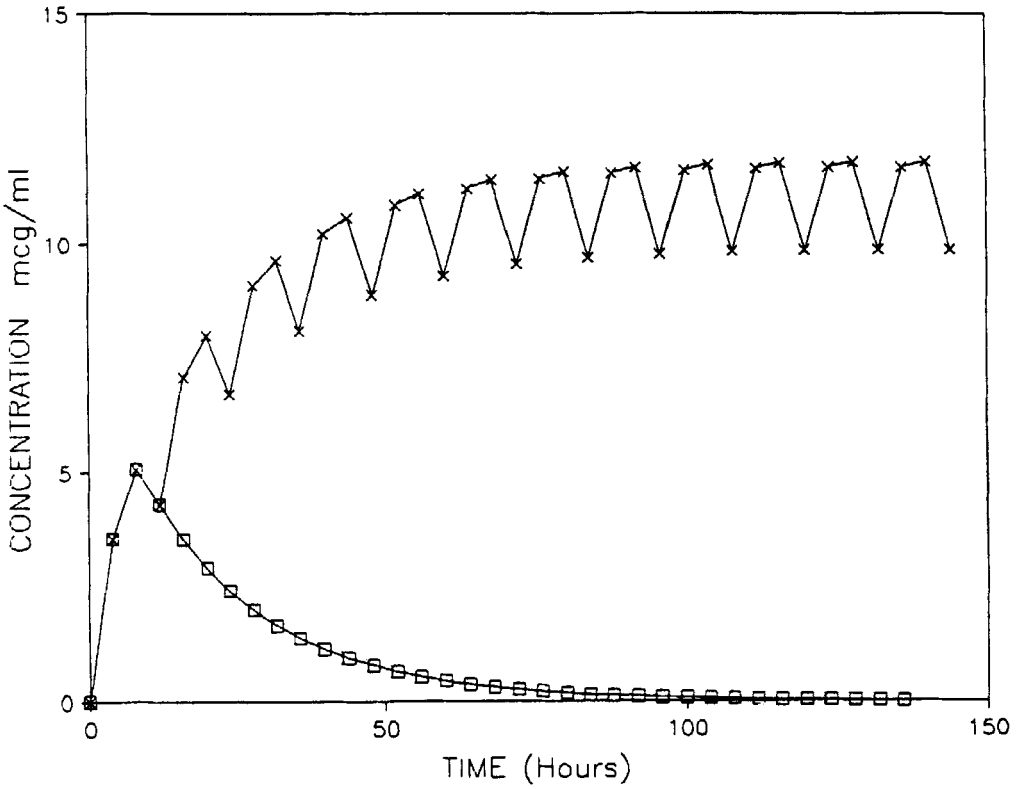

Fig. 2. Predicted serum theophylline concentration vs. time after administration of multiple doses at 12-hour intervals.

using the ESTRIP Computer Program[14] (four-exponential terms equation; best fit, R = 0.994, F = 0.33).

Apparent volume of distribution for theophylline (V_D) was given by:

$$V_D = \text{DOSE} / C_o$$

Plasma clearance (Cl) of theophylline was given by:

$$Cl = V_D K_{el}$$

Bioavailability of theophylline (fraction of dose absorbed was given by:

$$F = Cl \cdot AUCo \rightarrow \infty / \text{DOSE}$$

Table II. Weight control of the prepared tablets (mg)

	Form. I	Form. II	Form. IV	Form. V
1	327	340	480	492
2	334	364	506	500
3	329	353	499	490
4	328	365	490	500
5	330	368	503	496
6	327	370	495	494
7	326	365	493	500
8	325	348	510	495
9	330	345	485	497
10	332	356	492	502
11	327	372	503	497
12	334	380	503	497
13	334	354	495	496
14	331	359	506	500
15	331	378	487	500
16	327	350	490	498
17	329	385	492	496
18	333	343	492	490
19	326	376	490	492
20	328	357	499	495
$\bar{x}$	329	361	495	496
s	2.89	12.99	7.88	3.52
s_{rel}	0.88	3.59	0.38	0.71

Prediction of steady-state concentration. The predicted steady-state plasma theophylline concentration, C_{ss} for multiple dosage at 12-hour intervals was calculated by the equation

$$C_{ss} = F \cdot DOSE/Cl \cdot T$$

where T is the time intervals between the dosages. Fig 2 represents prediction based on absorption of single doses.

The fluctuation at the predicted steady-state theophylline concentration was calculated using the superposition principle[15].

% Fluctuation = (peak-through) coc 100/through coc

RESULTS AND DISCUSSION

All formulations were checked for their appearance. Formulation I and II gave good quality tablets. On the tab-

Table III. Content uniformity test (mg)

	Form. I	Form. II	Form. IV	Form. V
1	302	312	292	291
2	304	301	286	305
3	306	305	290	303
4	302	308	300	302
5	303	305	297	298
6	304	303	297	297
7	305	305	302	300
8	303	308	300	301
9	300	310	295	207
10	302	310	300	299
$\bar{x}$	303	307	296	300
s	1.73	3.46	5.15	2.80
s_{rel}	0.57	1.12	1.74	0.93

lets of formulations III, IV and V capping was observed, most of all in formulation III. Water content of granules was found 1%, and that of tablets 0.1%. Weight variation test[16] gave good results as it is shown in table II, except formulation III. Weight variation was within acceptable limits. Results of content uniformity are shown in table III. For formulations I and II there was a further content uniformity test for 1/2 and 1/3 of the tablet, (table IV).

Figure 3 shows the effect of granulation and figure 4 that of fillers on the dissolution rate of the tablets prepared. It appears that there is a significant influence of granulation, while no significant effect due to several fillers is observed. The results of the comparison of dissolution profiles of Theodur tablets with the controlled release theophylline tablets of formulation I in water media, are shown in fig. 5. Fig. 6 shows the dissolution profiles of 1/2

Table IV. Content uniformity test in parts of tablets

	Content in theophylline (in mg) of 1/2 tablet		1/3 tablet	
	Form. I	Form. II	Form. I	Form. II
1	158	159	111	107
2	156	160	102	110
3	158	158	107	109
4	144	148	95	100
5	147	148	100	99
6	146	150	101	100
$\bar{x}$	151	154	103	104
s	6.50	5.70	5.60	5.03
s_{rel}	4.30	3.70	5.43	4.83

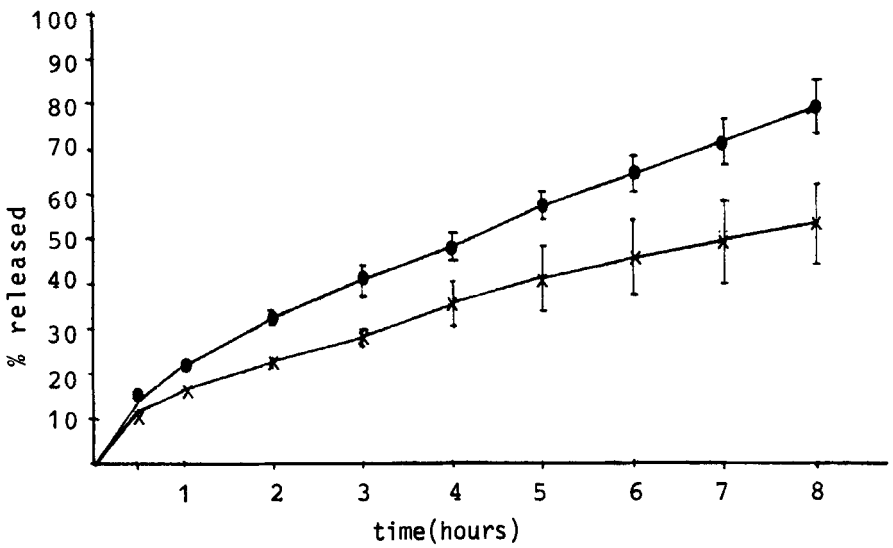

Fig. 3. Effect of granulation on dissolution rate of theophylline tablets. x: formulation I, ●: formulation II.

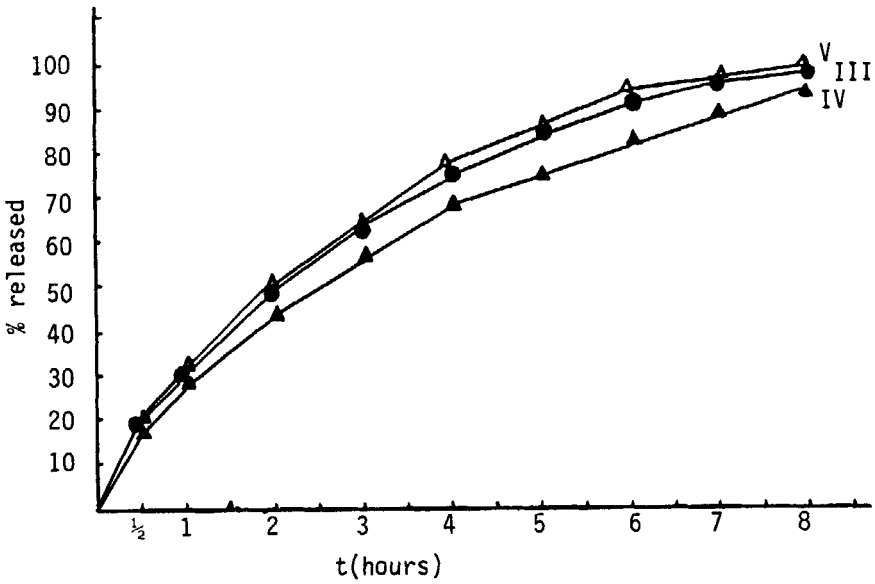

Fig.4. Effect of various fillers on dissolution rate of theophyllin tablets. ●:formulation III, ▲:formulation IV, Δ:formulation V

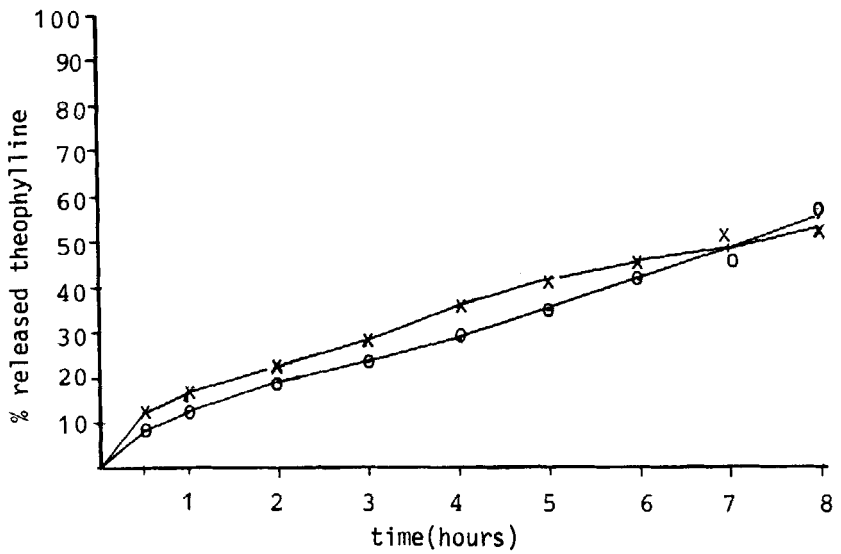

Fig. 5. Comparison of dissolution properties of theophylline from Theodur® (300mg)(o)and theophylline tablets of formulation I (x), in water media.

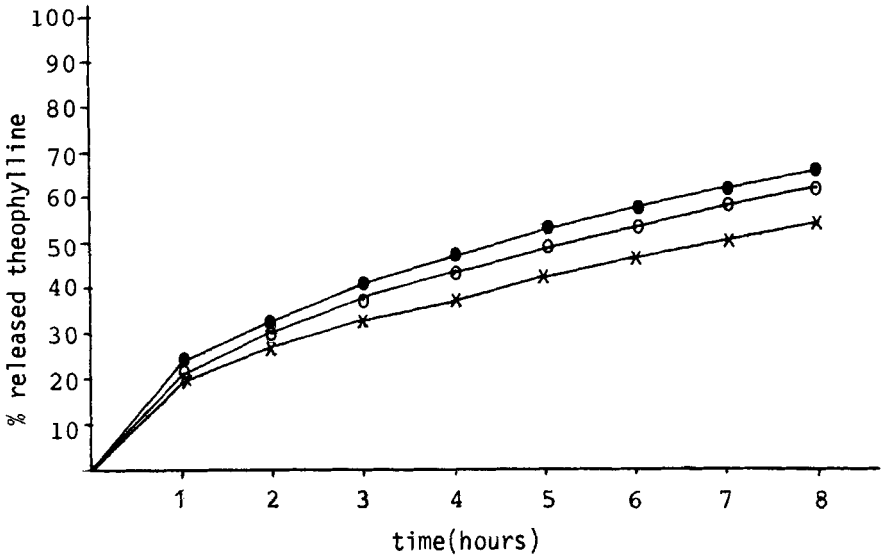

Fig. 6. Dissolution rate of formulation I. x: ½ tablet, ●: 1/3 tablet-middle part, o: 1/3 tablet-extreme part.

and 1/3 (middle and extreme part) of these tablets which are similar to those of the whole tablet.

From the view of pharmacokinetics, aththough pharmacokinetic data obtained in single dose studies are projected to simulate multiple dosage and may not present an actual situation, the results of our investigation show that the tablet if given at 12-hour intervals, BID, could achieve a stedy-state theophylline concentration of 11.2 µg/ml, a value which is very close to the ideal therapeutic least toxic concentration of 12.5 µg/ml. This value is vitrually identical to that of immediate release preparation[17, 18].

Since the width of therapeutic range is a ca 10 µg/ml, the fluctuation of the serum concentration must be less than 100%, to maintain the concentration with the therapeutic range throughout the dosing interval. After 12-hour dosing intervals predicted percent fluctuation is very low[19] and sug-

gest that tablet will maintain serun theophylline concentrations within the therapeutic range.

This novel tablet preparation possesses an appropriate release for use on a-twice-a-day basis, BID and demonstrates good relative bioavailability.

It is rapidly absorbed -short lag time- with a t_{max} which substantiates the slow release profile. Moreover, observed K_{el} indicates a decrease in theophylline elimination rate for healthy non-smoking adults -0.084 hr^{-1}- that has previously been reported[20].

CONCLUSIONS

The scope of our investigation was to demonstrate the sustained-release characteristics of this new tablet preparation configurated in a unique patented Dividose™ design. The dissolution profile of this tablet (formulation I), prepared with hydrohypropylcellulose after granulation was found very similar to that of a commercially available tablet (Theodur®). Analogous dissolution profiles are obtained from the 1/2 and 1/3 of the tablets.

An intraindividual inconcistency in theophylline absorption and other bioavailability parameters was expected and actually observed in this study. That intrasubject variation did not influence our calculations for the prediction of the steady-state concentration as they were based on total AUC and plasma theophylline clearance.

The mean fluctuation in theophylline concentration found in our volunteers taking a prescribed dose is very encouraging and promising because it implies more consistent bronchodilation drug activity.

The projected steady-state serum theophylline concentration based on single dose data theoretically supports the utilization of this theophylline sustained release tablet on a BID basis in patients requiring theophylline therapy.

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