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In vitro-in vivo correlation studies on a novel controlled release theophylline delivery system and on Theo-Dur tablets

D.L. Munday [a,*], A.R. Fassihi [b]

[a] *School of Pharmacy, The Robert Gordon University, Aberdeen, UK*
[b] *School of Pharmacy, Temple University, Philadelphia, PA, USA*

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Abstract

A good correlation should be obtained between data derived from in vitro dissolution and bioavailability studies on drug delivery systems if bioavailability parameters are to be reliably predicted from the in vitro dissolution variables. This study compares the in vivo absorption with the in vitro dissolution profiles into various dissolution media of a novel controlled release theophylline capsule (Mintab) containing mini-matrices, and also those of Theo-Dur 300 mg tablets. Mintab displayed significant pharmacokinetic advantages over Theo-Dur. However, Theo-Dur demonstrated good in vitro-in vivo correlation, whereas Mintab showed poor correlation.

Keywords: Controlled release; Theophylline; In vitro-in vivo correlation; Bioavailability

1. Introduction

The bronchodilating action of theophylline renders the drug useful in the chronic treatment of asthma. The therapeutic range for theophylline is narrow (10–20 μg/ml), although therapeutic effects may sometimes be achieved at plasma concentrations of 5–8 μg/ml (Jenne et al., 1972; Ellis et al., 1976). Toxic effects are frequent above 20 μg/ml (Jacobs et al., 1976). Therapeutic strategies aim therefore at achieving and maintaining average plasma concentrations within the therapeutic range, a strategy which is often difficult to achieve.

The sustained release oral formulations have emerged as the most useful preparations for maintenance therapy. However, the bioavailability of theophylline from these formulations may be incomplete and variable (Spangler et al., 1978; Weinberger et al., 1978). There is also considerable inter-subject variability in plasma concentration in different patients given the same dose due mainly to differences in absorption and rates of elimination (Hendeles et al., 1978; Ogilvie, 1978). There is a need therefore for dosage regimens to be carefully adjusted according to particular patient requirements. Although oral sustained release theophylline dosage forms are designed to control drug release rates, individual titration of the dose rate is still necessary. Presently available dosage units, however, cannot easily be divided

* Corresponding author. Fax +44-(224)-626559.

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into sub-units to meet the precise individual needs. This is especially the case with encapsulated pellets, although some tablets may be bisected or trisected.

A novel multiple-unit sustained release capsule containing mini-matrices of theophylline has been developed in our laboratories (Munday and Fassihi, 1989). Bioavailability studies have been conducted on this novel dosage form and then compared with those of Theo-Dur, a commercial product in tablet form containing 300 mg of anhydrous theophylline. Comparisons of the pharmacokinetic parameters revealed that the novel dosage form had distinct advantages over Theo-Dur.

However, bioavailability studies possess a number of inherent disadvantages including economic and ethical constraints. Therefore in vitro dissolution studies are extensively employed because of their simplicity and their lower cost. There must, however, be a good correlation between in vitro and in vivo characteristics (correlation coefficient $r > 0.9$) if the bioavailability parameters are to be reliably predicted from the in vitro dissolution variables. This study was undertaken to compare the absorption profiles obtained from in vivo evaluations utilising beagle dogs with the in vitro dissolution profiles of the novel sustained release capsule, as well as from Theo-Dur 300 mg tablets.

2. Materials and methods

2.1. Dosage forms

A new novel sustained release oral dosage form for theophylline (Mintab) consisting of hard gelatin capsules (size 1) each containing 20 mini-matrices (3 mm diameter, 15 ± 0.5 mg in weight) equivalent to a total of 300 ± 5 mg theophylline manufactured by a process described in earlier work (Munday and Fassihi, 1989). 10 of the mini-matrices were uncoated (immediate release 150 mg), while the other 10 were film coated with Eudragit RL 2% w/w (sustained release 150 mg).

A commercially available product, Theo-Dur 300 mg tablets, from Rio Ethicals was also studied.

2.2. Dissolution studies

The in vitro dissolution of theophylline from the encapsulated mini-matrices and the Theo-Dur 300 mg tablets was determined in triplicate by the USP XXII paddle method utilising a Hanson Dissolution Drive Control and Multiple Spindle Drive (Northridge, CA). The dissolution media used (900 ml) were distilled water, dilute HCl (pH 1.2 and 5.3), dilute NaOH (pH 7.4) and phosphate buffers (pH 5.3 and 7.4) at 37 ± 0.5°C. The paddles were rotated at a speed of 50 ± 1 rpm. Samples of dissolution medium were removed at regular time intervals, diluted appropriately, and assayed for theophylline by UV spectrophotometry at 271 nm using a Shimadzu UV-160A spectrophotometer (Shimadzu Corp., Kyoto, Japan). An equal volume of dissolution medium at 37°C was added to maintain constant volume.

2.3. Bioavailability studies

Four beagle dogs weighing 12–15 kg (13.78 ± 1.72 kg) were used in this cross-over design single dose study on each test unit after a suitable wash-out period (14 days). The dogs were fasted for 24 h before administration of the first test dose with water ad libitum. A test unit was administered between 06:00 and 07:00 h on the day of the study. Oral administration of the unit was achieved by a method similar to that described by Gangadharan et al. (1987). The dogs received their normal food on the day of the study.

Blood samples were drawn at 0, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h after dosing. About 3–5 ml of blood was drawn each time from the jugular vein and collected into Vacutainer tubes (Vacutainer Systems, Rutherford, NJ, USA). The blood samples were allowed to stand for 1 h, centrifuged and serum kept frozen (−20°C) until analysis. Theophylline concentrations in the serum were determined using a fluorescence immunoassay system (TDX Analyser, Abbot). The area under the curve (AUC) was calculated using the linear trapezoidal rule. The extent of bioavailability (EBA) was determined by comparison with the serum concentration curve obtained after oral

administration of 300 mg of encapsulated anhydrous theophylline powder.

3. Results and discussion

The mean serum concentration-time curves for Mintab and Theo-Dur are shown in Fig. 1.The new novel sustained release capsule (Mintab) was demonstrated to have significant advantages over Theo-Dur as seen from the various calculated pharmacokinetic parameters (T_{max}, C_{max}, MRT, T_{75} and EBA) shown in Table 1. The dosage form Mintab also provided for precise dosage titration for individual patient needs by allowing for the adjustment of the exact number of individual mini-matrices within the hard gelatin capsule. In addition to the well known advantages of multiple-unit dosage forms over single-unit dosage forms, the use of pressed mini-matrices, compared with pellets manufactured by extrusion, would result in significant savings in costs over the long term as has been previously shown (Ney, 1991).

In the in vivo evaluation studies, the percentage of drug absorbed was calculated from the

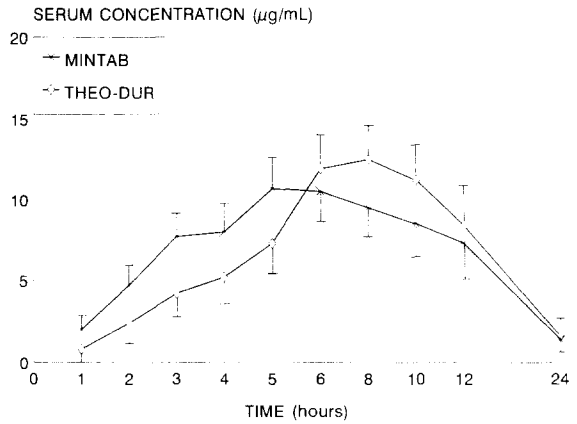

Fig. 1. Mean theophylline concentrations (±S.D.) as a function of time in serum following peroral administration of 1 dosage unit of Mintab and Theo-Dur ($n = 4$).

fraction of the area under the curve (AUC) at each time interval. At time t, the percentage of drug absorbed was calculated using the Wagner-Nelson analysis (Wagner and Nelson, 1964).

$$\% \text{ absorbed} = \frac{\dfrac{C(t)}{Ke} + \text{AUC}^{0 \rightarrow t}}{\text{AUC}^{0 \rightarrow \infty}} \times 100$$

Table 1
Pharmacokinetic parameters obtained after administration of the two sustained release preparations, Theo-Dur 300 mg and the encapsulated mini-matrix preparation (Mintab) containing the equivalent of 300 mg theophylline

	Dog				Mean ± S.D.
	1	2	3	4	
MRT (h)					
Mintab	10.4	9.2	12.8	18.6	12.7 ± 4.2
Theo-Dur	5.8	9.3	6.9	7.1	7.3 ± 1.5
T_{max} (h)					
Mintab	6.0	6.0	5.0	5.0	5.5 ± 0.6
Theo-Dur	6.0	8.0	10.0	8.0	8.0 ± 1.6
C_{max} (μg/ml)					
Mintab	11.1	15.7	10.9	6.2	11.0 ± 3.9
Theo-Dur	18.7	11.8	13.4	9.6	13.4 ± 3.9
T_{75} (h)					
Mintab	6.4	5.2	7.1	9.5	7.1 ± 1.8
Theo-Dur	2.4	6.0	3.1	5.7	4.3 ± 1.8
EBA (%)					
Mintab	83.2	107.2	100.2	94.6	96.3 ± 10.1
Theo-Dur	75.1	80.0	78.1	79.3	78.1 ± 2.2
$F_{Mintab}/F_{Theo\text{-}Dur}$	1.11	1.34	1.28	1.19	1.23 ± 0.10

MRT, mean residence time (time in h corresponding to 63.2% elimination); T_{max}, time at which the maximum serum concentration is reached; C_{max}, maximum drug serum concentration; T_{75}, time period during which drug concentration exceeds a value of 75% of C_{max}; EBA, extent of bioavailability (compared to orally administered powdered drug); $F_{Mintab}/F_{Theo\text{-}Dur}$, relative absorption efficiency of Mintab compared to Theo-Dur.

The mean half-life of theophylline from Mintab (6.8 h) was found to be not significantly different from the documented half-life of theophylline (5.5 h) (Ritschel, 1986) and therefore absorption was not rate-limiting. The Wagner-Nelson equation provides a means of estimating the absorption when there is a monoexponential decline describing the elimination of the drug.

A comparison of the absorption profiles of theophylline obtained in vivo and the release profiles obtained from in vitro experiments using Theo-Dur 300 mg tablets is shown in Fig. 2a and b. Fig. 2a shows the in vitro release and in vivo absorption of theophylline plotted against real time, whereas Fig. 2b depicts the plots after a correction for differences in the length of the start-up period (2 h). This period is the time taken for water to penetrate the system, dissolve the drug and then for the drug solution to diffuse slowly outwards. These corrected comparisons are very useful to validate the in vitro tests. The in vitro release of theophylline from Theo-Dur tablets was not affected by the pH or constituents of the dissolution media used. The dissolution data obtained for each medium were within 5% limits compared to the dissolution into distilled water.

The in vitro and the in vivo curves for Theo-Dur tablets (Fig. 2b) follow each other reasonably closely. The in vitro release rate correlates well with the rate at which the drug is absorbed, although in the corrected graph (Fig. 2b) the in vitro dissolution was slightly faster during the first 6 h. Thereafter, the in vivo absorption was slightly more rapid. Moreover, the biphasic profile of the dissolution curve for Theo-Dur was not reflected in the absorption curve.

On the other hand, the in vitro release and in vivo absorption profiles for the new novel sustained release dosage form (Mintab) show poor correlation as seen in the corrected plots (Fig. 3). Over 90% of the drug was released in vitro within 6 h using distilled water, dilute HCl (pH 1.2 and 5.3) and dilute NaOH (pH 7.4). However, in vitro drug release into media containing phosphate ions (pH 5.3 and 7.4) was very slow over the 12 h sampling period. The maximum amount of drug released after 12 h was approx. 20 and 30% of the total drug content in pH 5.3 and 7.4, respectively. The reasons for this impeded release into phosphate buffers have been presented in our earlier work (Fassihi and Munday, 1989). The composition and pH of the dissolution medium are therefore important factors in determining the rate of in vitro release.

Theo-Dur tablets demonstrate good in vitro-in vivo correlation under these conditions of testing. According to information from the manufacturer of Theo-Dur, about 35% of the drug is present in a matrix and the remainder is contained in small

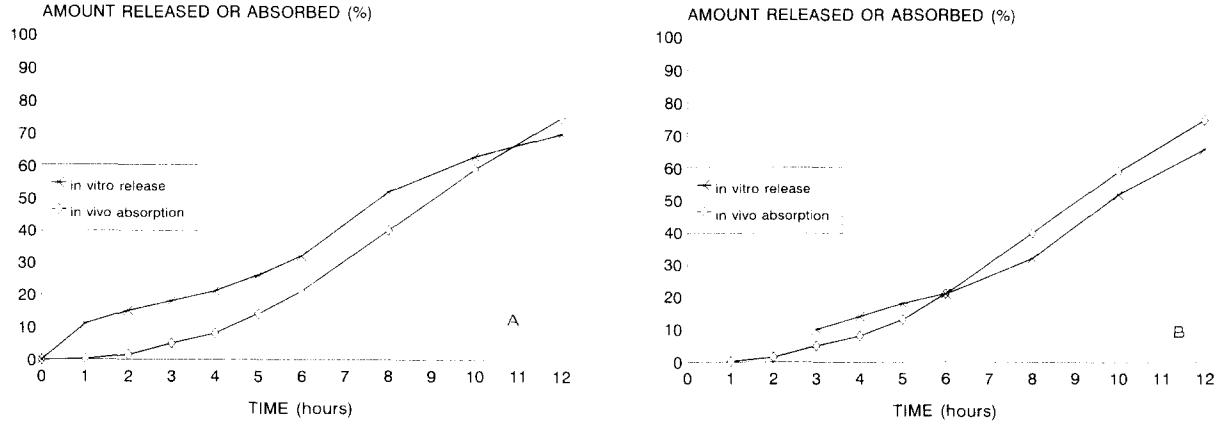

Fig. 2. (a) In vitro release of theophylline from Theo-Dur 300 mg tablets compared to the in vivo absorption plotted against real time. The in vitro parameter (% of dose) is the amount of drug dissolved and the in vivo parameter is the total amount of drug absorbed (Wagner-Nelson analysis). (b) In vitro release and in vivo absorption of theophylline from Theo-Dur 300 mg tablets after a 2 h correction for differences in length of the start-up period.

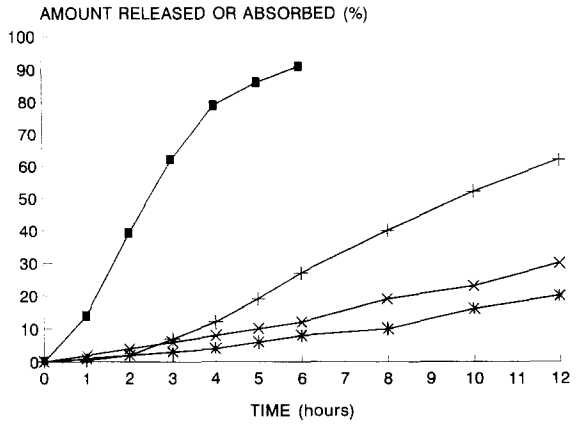

Fig. 3. In vitro release and in vivo absorption profiles of theophylline from the new sustained release capsule dosage form containing film coated mini-matrices (Mintab). (■) In vitro release into water, dilute HCl (pH 1.2 and 5.3) and dilute NaOH (pH 7.4); (+) in vivo absorption; (*) in vitro release into phosphate buffer (pH 5.3); (×) in vitro release into phosphate buffer (pH 7.4).

cores which are imbedded in the matrix. For this design of tablet it is possible to predict fluctuations in drug plasma concentrations on the basis of in vitro dissolution behaviour. In the case of the new sustained release system (Mintab), the in vitro-in vivo correlation is poor. This is a diffusional system consisting of a drug core (mini-matrix) evenly coated with a permeable polymer film coating. It is apparent that drug release in vivo by diffusion takes place at a much slower rate than in vitro dissolution into water, but at a faster rate than in vitro dissolution into phosphate buffers, using the USP XXII paddle apparatus. This diffusion release mechanism does appear therefore to depend greatly on the composition of the medium into which the drug is released. The constituents of the gastrointestinal fluids must therefore influence and determine the rate of diffusion of theophylline through the polymer film coat in the in vivo model.

A complex relationship exists between in vitro dissolution results generated in the pharmaceutical laboratory and in vivo bioavailability results generated in the clinical setting. Correlations apply only to the specific products studied. A new formulation may not relate to the previously demonstrated correlation. The use of in vitro dissolution data to predict explicitly the overall drug absorption process is dictated by the operating release mechanism, and is limited.

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