BIOPHARMACEUTICS & DRUG DISPOSITION
Biopharm. Drug Dispos. **19**: 517–522 (1998)

Pharmacokinetic Evaluation in Dogs of Theophylline in a Novel Zero-Order Release Core-in-Cup Tablet

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ABSTRACT: A new core-in-cup tablet that is manufactured from a novel adjustable punch, has been formulated and evaluated for its ability to release with subsequent absorption of theophylline via a zero-order rate of absorption. The core-in-cup tablets were compared with core only tablets and immediate release capsules. Pharmacokinetic parameters used to test the effectiveness of the formulations included, elimination rate, rate and kinetic order of absorption, relative availability as compared with an immediate release capsule of pure theophylline, and percentage area under the curve fluctuation (%AUCF) at steady state. The correlation coefficient, Akaike's information criterion (AIC) and the *F*-ratio probability were used to test the applicability of a zero-order, first-order, or square root of time model, for the rate of release of theophylline from the core-in-cup and core only tablets. The zero-order rate model was most applicable to the core-in-cup tablet, whereas the square root of time release model was most applicable to the core only tablet. The average %AUCF for the core-in-cup tablet was 9.26 ± 3.15 while that for the core only tablet was 16.19 ± 2.37 ($p = 0.0545$). The results of this study suggest that the core-in-cup tablet is a versatile zero-order release rate dosage form that are simple to produce. © 1998 John Wiley & Sons, Ltd.

Key words: zero-order release; theophylline; core-in-cup tablet; pharmacokinetics; dog

Introduction

There are many controlled release oral drug delivery systems on the market today, most of which consist of simple compressed matrices incorporating active drug homogenously mixed together with a hydrophillic polymer or mixture of polymers. Because of the biconvex shape of the average tablet it is theoretically impossible for these tablets to release the active drug from it at a zero-order rate. Whether the matrix releases drug via swelling control or erosion (or both), it is almost impossible to achieve a zero-order release. Most of these matrix-type tablets release drug according to the square root of time kinetics [1,2]. However, some success has been achieved with theophylline by use of pelletization technology which is then compressed into a matrix tablet [3,4]. These systems have been found to release theophylline at an apparent zero-order rate of release.

An effective means of changing the release kinetics from matrix systems is to change the geometry of the matrix. The geometry must be changed to provide a constant releasing area to the dissolution fluid, i.e. release from one side of a flat tablet, slab, base of cylinder, or inwardly releasing hemisphere. A number of such systems have been tested. Hsieh *et al*. [5] produced inwardly releasing hemispheres of sodium salicylate in polyethylene, and bovine serum albumin in ethylene vinyl acetate matrices, which were coated with paraffin. Zero-order release in saline at a rate of 0.5 mg day^{-1} was achieved for 60 days. This system however, is difficult to manufacture and consists of a number of intricate steps in its production.

Devi *et al*. [6] developed zero-order release matrix tablets of oxprenolol hydrochloride. Zero-order release was accomplished with swelling and erosion control of the polymer matrix. This system unfortunately, is only applicable to drugs that have similar solubility characteristics of oxprenolol hydrochloride, as they rely on solubilization and then diffusion out of the matrix.

Seta *et al*. [7] prepared core-in-cup compressed tablets of disc-shaped bilayer core matrices of captopril and hydroxypropyl cellulose (HPC) surrounded on the bottom surface and circumference wall (the cup) with an inactive mixture of ethylcellulose and carnauba wax. The two layers of the core contained different concentrations of captopril. It was found that this type of system released captopril *in vitro* at a zero-order rate over a period of 3–6 h. The core-in-cup tablets were produced by means of first compressing out the active core on a single punch

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CCC 0142–2782/98/080517–06$17.50

Received 18 August 1997
Accepted 30 March 1998

tabletting press using round flat face punches to form a disc. The disc was then placed by hand in the centre of a larger round flat face punch in the die cavity of the press, filled with the inert polymer mixtures, and then compression coated by hand at high pressure. To place the core in the centre of the round flat punch called for careful and tedious placement and judgement. The problem with this compression coated method is that it cannot be automated and does not produce an even, elegant tablet. Both these properties are needed for commercial production of tablets.

In order to produce a tablet that could release a number of model drugs of varying solubilities at a zero-order rate of release in a reproducible manner, we have formulated a novel core-in-cup tablet that can be produced in an automated fashion from an adjustable inner rod punch. The core-in-cup system has released a number of model drugs like caffeine, ibuprofen and theophylline *in vitro* at a zero-order rate of release [8–10]. The purpose of this study, therefore, was to evaluate the pharmacokinetic release and absorption of theophylline model drug *in vivo* in beagle dogs.

Many different criteria have been used to assess the performance of sustained-release drug delivery systems [11]. These range from simple mean absorption time (MAT) as a measure of absorption to many different measures of drug plateau time variation, both after single and multiple dosing regimens. Regardless of the criteria used, the rate of absorption and peak drug level characteristics, like peak plasma time and plasma drug fluctuation, are the major *in vivo* pharmacokinetic properties of drug delivery systems that need to be analysed. The purpose of this study therefore, is to conduct an *in vivo* pharmacokinetic study, using theophylline as a model drug for the core-in-cup tablets to measure the absorption rate and peak plasma fluctuation. Pharmacokinetic parameters that will be studied, include, elimination rate, rate and kinetic order of absorption, relative bioavailability, and %AUCF at steady state. These parameters were measured for both compression coated core-in-cup tablets as well as core only matrix tablets.

Experimental Section

Materials

Acacia was supplied by Saarchem (Pty) Ltd, South Africa. The acacia had a viscosity of 53 cps as a 4% aqueous solution at 23°C. Theophylline anhydrous (Knoll AG, Germany) and caffeine (Sigma Chemical Company, USA) were ground in a mortar and the fraction passing through a No. 150 standard UK sieve was used. Sodium-1-octanesulfonate and sodium-1-heptanesulfonate were supplied by TCI-Ace, Tokyo Kasei Kogyo Company, Ltd., Japan. Ethylcellulose (Riedel de-Haën, South Africa) and carnauba wax (Sigma Chemical Company) were also used as supplied. All other reagents used were standard laboratory grade.

Formulations

Three different dosage forms of theophylline were assessed during the *in vivo* study. Capsules containing 100 mg theophylline were prepared by means of separately weighing out 100 mg theophylline and filling size 2 capsules. The capsules were used as the immediate release dosage form from which the theophylline elimination rate could be calculated. Its blood profile was also used to determine the relative bioavailability of the core-in-cup and core only tablets. Core-in-cup and core only tablets containing 53.846 mg (35% w/w) acacia and 100 mg theophylline per tablet were also prepared and made as previously described [9].

Drug Administration and Sample Collection

Five female adult Beagle dogs, clinically healthy and hematologically normal, weighing between 16 and 22 kg, were used in this study. Each of the three dosage forms were given to each of the dogs on different days, separated by a 14 day 'wash out' period, over a period of 3 months. Food, but not water, was withheld for 12 h before and after drug administration. Dosing of each dog was staggered at 15 min intervals so as to facilitate subsequent blood sampling. Oral administration of the drug delivery systems was achieved by opening the mouth of the dog, depressing the tongue, placing the drug delivery system in the throat region with subsequent administration of about 100 mL of water. The mouth was firmly closed and air was blown through the dog's nose in order to facilitate swallowing. Blood samples (4–5 mL) were withdrawn from the jugular vein at 0, 0.5, 1, 2, 4, 6, 8, 10, 16 and 24 h. The blood samples were allowed to stand for 1 h, centrifuged at $1100 \times g$ in a Hettich EBA III centrifuge (Tuttlingen, Germany) for 15 min, and then stored at 4°C until analysis. All samples were analysed within 48 h from collection. The faeces of each dog was collected and checked for the presence of the cup portion of the tablet.

Theophylline Extraction and Analysis

A 1 mL sample of blood plasma was mixed with 1 mL of caffeine internal standard solution (5 μg mL^{-1}) on a vortex mixer for 1 min. The theophylline and caffeine were then extracted according to the method of Davis *et al*. [12]. The accuracy and reproducibility from spiked drug-free plasma were calculated from concentrations of 7.5, 1.875 and 0.4688 μg mL^{-1} of theophylline in plasma

by comparing the peak-height ratio against internal standard with those obtained for aqueous solutions containing known concentrations of theophylline. The mean extracted concentrations ($n = 3 \pm$ S.D.) calculated on the basis of peak-height ratios against the internal standard were 7.1576 ± 0.7157, 1.4868 ± 0.1891 and 0.4854 ± 0.1009 μg mL^{-1} for the 7.5, 1.875 and 0.4688 μg mL^{-1} spiked plasma solution of theophylline, respectively.

Theophylline/internal standard solutions were analysed on a 15 cm Beckman ultrasphere ODS 5 μm column connected to a Beckman System Gold HPLC consisting of a 126 programmable solvent module and 168 diode array detector module. Analytical wavelength was set at 280 nm. The mobile phase was perfused through the column at 1 mL min^{-1} and consisted of 95% v/v 0.02 M sodium acetate buffer adjusted to pH 4.0 with concentrated acetic acid, 0.5% w/v sodium-1-heptanesulfonate, 0.5% w/v sodium-1-octanesulfonate, and 5% v/v propan-1-ol. Chromatograms for theophylline and caffeine (internal standard) were completed within 10 min. Quantification of theophylline levels were based on comparison with standard solution curves. The detection limit using this method was approximately 0.2 μg mL^{-1} theophylline.

Data Analysis

The plasma concentration–time curves for the core-in-cup and core only systems were analysed to estimate the rate of absorption, the %AUCF and the relative bioavailability (%RA).

The rate of absorption was estimated from the Wagner–Nelson method [13,14]. This method has gained wide acceptance because it does not require prior estimation of the apparent volume of distribution and places no limitations on the order of the absorption rate constant. It is only applicable to one compartment models. This limitation, however, is not a problem when using the technique for absorption studies when comparing drug delivery systems. Equation (1) was derived by Wagner and Nelson for estimation of the percentage absorption of drug from a drug delivery system up until time T.

$$\%\ \text{absorbed} = \frac{A_T}{A_\infty} \times 100 = \frac{C_T + K(\text{AUC})_T}{K(\text{AUC})_\infty} \qquad (1)$$

where, A_T is the cumulative amount of drug absorbed from time zero to time T; A_∞ is the amount eventually absorbed; K is the overall elimination rate constant; C_T is blood, serum, or plasma concentration at time T; $(\text{AUC})_T$ is the area under the curve up until time T; and $(\text{AUC})_\infty$ is the area under the curve up until infinity.

These rates of absorption for each dog and drug delivery system were then checked to see how well they fit either a zero-order (plasma concentration versus time), first-order (logarithm of plasma concentration versus time), or square root of time (plasma concentration versus square root of time) model. In order to check the applicability and 'goodness of fit' of each model, Akaike's information criterion (AIC) [15], the F-ratio probability [16], and correlation coefficient for each model was calculated. In general, the smaller the AIC and F-ratio probability, the more applicable the model is. F-ratio probabilities of less than 0.01 were judged to be indicative of the model being significant for the drug delivery system at the 99% level of confidence. The closer the correlation coefficient is to 1.0 the more applicable the model is. For all the models, the residual sum of squares was calculated using Statsgraphics version 5 (Statistical Graphics Corporation, USA). Data used to calculate the 'goodness of fit' criteria were taken from the fraction of theophylline absorbed from time zero to 4 h (the linear portions of the fraction absorbed versus time plots). The results from each dog were analysed separately because there is usually quite a large subject to subject variation in the blood levels of theophylline, as well as the fact that the dogs were not dosed on a quantity per kg basis. The elimination rate used to calculate the fraction of drug absorbed for each time interval in Equation (1) was estimated from the last section (time 10–24 h) of the plasma concentration–time curve after the immediate release capsule dose.

The method suggested by Boxenbaum [17] was used to calculate the %AUCF. This method is a robust method, as it utilizes all the plasma blood levels measured to calculate the fluctuation. The lower the %AUCF at steady-state, the better the controlled-release behaviour of the drug delivery system, and the closer the rate of release is to being described by a zero-order rate of release. To estimate the %AUCF at steady state, the plasma concentrations after a single dose were extrapolated to the time interval between 50 and 60 h using the method of superposition [18–20] based on a 10 h dosing interval. The concentration remaining at each time interval from the previous intended dosage (C_r) was calculated from Equation (2). This equation is based on the first order elimination rate calculated previously.

$$C_r = C_{T-1}\, e^{K_e(T-T-1)} \qquad (2)$$

The estimated values of plasma concentration at steady state were based on a dosing interval of 10 h. This shorter dosing interval from the intended 12 h dosing interval, was used as the gastrointestinal transit time of dogs is shorter than that of humans [21]. To calculate the %AUCF below and above the average plasma concentration, the intersection point of the graph at the average plasma concentration level was estimated graphically.

Calculation of %AUCF was calculated from Equation (3).

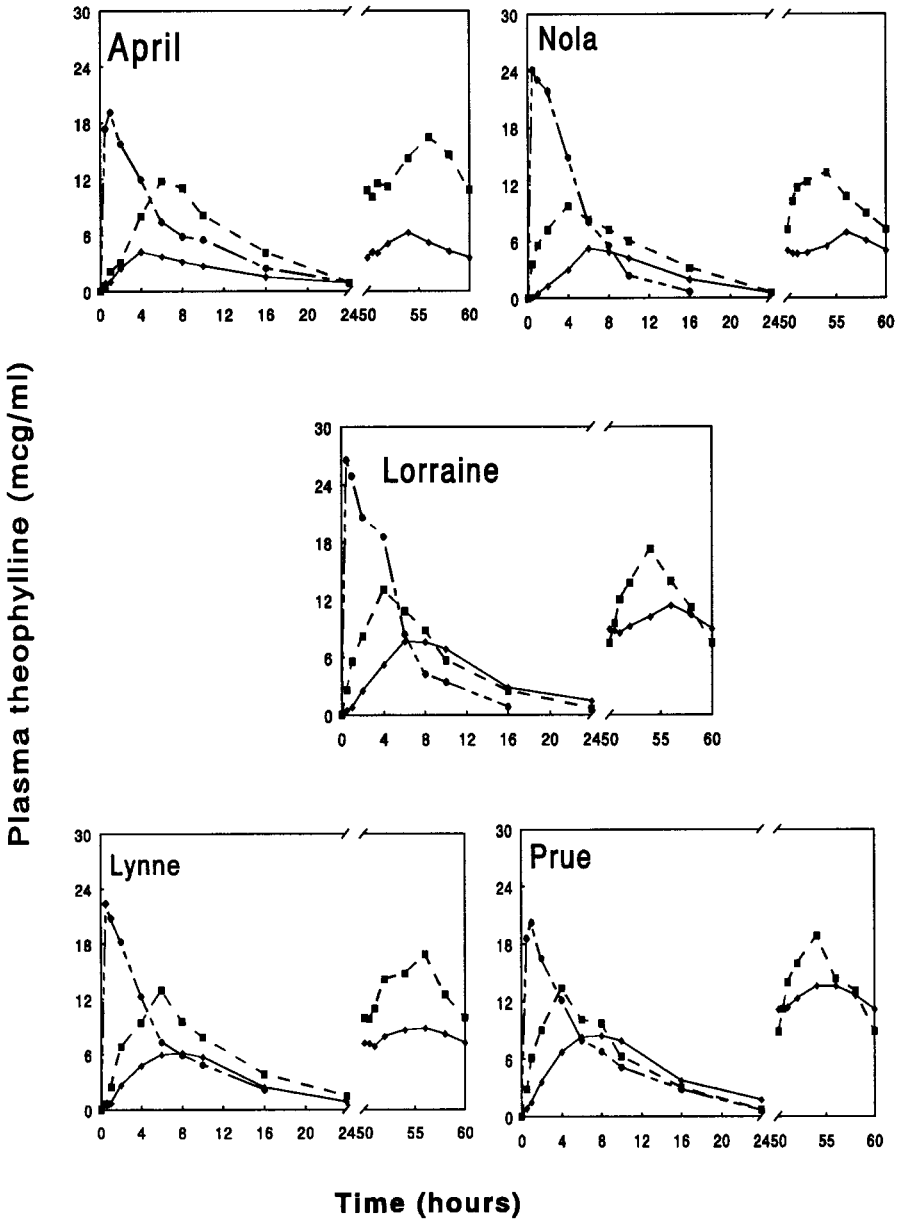

Figure 1. Theophylline plasma concentrations from capsules, core only tablets and core-in-cup tablets in beagle dogs. ●, capsule; ■, core only tablet; ◆, core-in-cup tablet

$$\%\text{AUCF} = 100 \times \frac{\text{AUC (above } C_{av}) + \text{AUC (below } C_{av})}{\text{AUC}} \quad (3)$$

The percentage relative availability of the core-in-cup tablets were calculated using Equation (4).

$$\%\text{RA} = \frac{\text{AUC}_{\text{core-in-cup}}}{\text{AUC}_{\text{capsule}}} \times 100 \quad (4)$$

To test whether there is a significant difference between the core only and core-in-cup drug delivery systems, a single paired-sample hypothesis test at a 95% confidence interval was tested on the difference in the parameter that was measured. A single paired-sample hypothesis test is used because the two drug delivery systems were each given to each dog in the study as a cross-over regimen.

Results

Figure 1 shows the theophylline plasma concentrations of the three dosage forms given to each dog. The extrapolated theophylline plasma concentrations to the steady state time interval of 50–60 h is also shown. As can be seen from the graphs, there is quite a large variation in the plasma concentrations from dog to dog. The variation, however, between the three dosage forms in each dog is much more consistent than the variation between the dogs. This is also the case with the elimination rate calculated from the capsule dosage form, which varies from 0.1223 to 0.1803 h^{-1}.

Table 1 lists the results from the calculation of the relevant parameters of AUC, %AUCF, and the %RA for the absorption of theophylline from the cap-

Table 1. Relevant pharmacokinetic parameters of the *in vivo* theophylline analysis from capsules, core only tablets and core-in-cup tablets

Parameter	Nola	April	Lorraine	Lynne	Prue	Mean ± S.D.
Mass (kg)	19.7	14.7	19.0	11.6	13.5	
Capsules						
AUC	146.89	139.21	144.83	134.64	135.70	140.25 ± 4.86
K_e (h^{-1})	0.1803	0.1400	0.1446	0.1555	0.1223	0.1485 ± 0.0192
Core only						
AUC	166.02	132.84	126.15	139.91	134.58	129.90 ± 8.21
%AUCF	15.49	12.69	19.97	15.65	17.14	16.19 ± 2.37
%RA	78.99	95.43	87.10	103.91	99.17	92.92 ± 8.88
Core-in-cup						
AUC	61.27	51.51	98.02	81.03	117.98	81.96 ± 24.13
%AUCF	8.81	15.40	8.02	7.38	6.67	9.26 ± 3.15
%RA	41.71	37.00	67.68	60.18	86.94	58.70 ± 18.11

sules, core only and core-in-cup tablets. Table 2 lists the correlation coefficients, AIC values, and *F*-ratio probabilities (those of $p < 0.01$) for the different models from the core only and core-in-cup tablets.

Discussion

Theophylline from the core-in-cup tablet was absorbed *in vivo* at a rate that is best described by a zero-order model. This is evidenced from the higher mean correlation coefficient (0.9952 ± 0.0017), and the low mean values for the AIC (-24.95 ± 2.88) and the *F*-ratio probabilities. The absorption of theophylline from the core only tablet was best described by the square root of time model. The mean AIC of -20.92 ± 3.96 was the lowest for the square root of time model. The *F*-ratio probabilities for the square root of time model were also significant for all dogs except April (for which no model was applicable at the 99% level). For core only tablets, it was found that the correlation coefficient for the zero-order model (0.9902 ± 0.0034) was slightly higher than the correlation coefficient

Table 2. Correlation coefficients, AICs, and *F*-ratio probabilities ($p < 0.01$) for the different models from core only and core-in-cup tablets

Model	Nola	April	Lorraine	Lynne	Prue	Mean ± S.D.
Core only						
Order of release correlation coefficient						
0-order	0.9887	0.9875	0.9963	0.9870	0.9917	0.9902 ± 0.0034
1-order	0.9218	0.8943	0.9034	0.8553	0.8922	0.8934 ± 0.0217
$\sqrt{t}$	0.9979	0.9447	0.9875	0.9669	0.9881	0.9770 ± 0.0191
AIC values						
0-order	−22.11	−19.18	−20.57	−17.78	−16.90	−19.51 ± 2.45
1-order	−3.90	−4.83	−8.63	−2.30	−8.37	−5.61 ± 2.80
$\sqrt{t}$	−25.02	−14.92	−19.15	−22.62	−22.93	−20.92 ± 3.96
F-ratio probabilities (* $p < 0.01$)						
0-order	*	—	*	—	*	
1-order	—	—	—	—	—	
$\sqrt{t}$	*	—	*	*	*	
Core-in-cup						
Order of release correlation coefficient						
0-order	0.9938	0.9957	0.9955	0.9930	0.9980	0.9952 ± 0.0017
1-order	0.8931	0.9403	0.9309	0.9229	0.9295	0.9233 ± 0.0161
$\sqrt{t}$	0.9494	0.9689	0.9526	0.9580	0.9673	0.9592 ± 0.0078
AIC values						
0-order	−26.76	−21.44	−25.32	−22.75	−28.49	−24.95 ± 2.88
1-order	−2.77	−11.91	−7.91	−7.23	−8.98	−7.76 ± 3.31
$\sqrt{t}$	−19.08	−15.18	−17.97	−17.69	−18.35	−17.65 ± 1.48
F-ratio probabilities (* $p < 0.01$)						
0-order	*	*	*	*	*	
1-order	—	—	—	—	—	
$\sqrt{t}$	—	—	—	—	—	

(0.9770 ± 0.0191) for the square root of time model. Therefore, one can conclude that the results indicate that theophylline is released from the core-in-cup tablet at a zero-order rate of release and is subsequently absorbed at a zero-order rate of absorption. On the other hand, the core-only matrix type tablet releases drug at square root of time rate of release and is hence absorbed at this rate.

Although the average %AUCF for the core-in-cup tablet was less than that from the core only tablet, the difference of 6.9334 was not significant at the 95% level. The probability of a significant difference was $p = 0.0545$. This is probably due to the %AUCF for the core-in-cup tablet given to one of the dogs (April) was slightly greater than that for the core only tablet.

As could be expected, the %RA of theophylline from the core only and core-in-cup tablets were significantly different ($p = 0.0147$). There was also quite a large variation in the AUC and hence %RA from animal to animal. The difference in the %RA of theophylline from the core only and core-in-cup tablets was due to the average short gastrointestinal transit time of the dogs. In three of the five dogs, a cup tablet with a small amount of remaining core, was found in the faeces of the dogs. The intact cups were found after 6 h for Nola and after 8 h for April and Lynne. The empty cups for the two remaining dogs were found in the faeces some time after 16 h. For all the dogs, the cup portion of the core-in-cup tablet was defecated intact. The only visible change to the cups were a slight rounding off and erosion around the edges of the cups.

Based on the results we have obtained previously from an *in vitro* study [22], as well as the *in vivo* results obtained in this study, we believe that the core-in-cup tablet is a versatile drug delivery system for delivery of drugs at a zero-order rate. It is also simple to manufacture and is consistently reproducible. This is because it is manufactured on automated equipment that replicates the formulation perfectly each and every time. The core-in-cup tablet is applicable to a large range of drugs with differing physicochemical properties. All that is required, is to match the drug with a suitable erodible polymer to release the drug over a 12 h period. The core-in-cup system is also useful for loading dose bilayer tablets as well as the formulation of pulsatile multiayer tablets.

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