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RESEARCH PAPER



# Zero-Order Release of Theophylline from a Core-in-Cup Tablet in Sequenced Simulated Gastric and Intestinal Fluid

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## ABSTRACT

*Core-in-cup tablets containing theophylline were evaluated for their dissolution characteristics in sequenced simulated gastric fluid (SGF) followed by simulated intestinal fluid (SIF). Core-in-cup tablets containing 10% w/w, 20% w/w, and 30% w/w acacia as binder were evaluated for their effects on the time course of release of theophylline. This was done to optimize a formula that could release theophylline at a zero-order rate of release for 8–16 hr in simulated gastrointestinal fluids. Theophylline was released and dissolved from the core-in-cup tablets at a rate that is more consistent with a zero-order dissolution rate than a first-order dissolution rate in both SIG and SIF. The dissolution rates of theophylline from the 10%, 20%, and 30% acacia core-in-cup tablets were 0.87 mg/min, 0.53 mg/min, and 0.27 mg/min, respectively in SGF, and 0.61 mg/min, 0.30 mg/min, and 0.20 mg/min, respectively in SIF. The results indicate that a concentration of 32% w/w acacia in the core tablet will release theophylline at a rate of 0.14 mg/min in SGF for 2 hr followed by SIF for 10 hr.*

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## INTRODUCTION

To ensure that new controlled release drug delivery systems release drug at a controlled rate throughout the gastrointestinal tract (GIT) following oral administration, it is essential in the development stages to use dissolution methods that allow pharmacokinetic screening of dosage forms. For drugs that are well absorbed, the rate of release is an important parameter. To predict the in-vivo release of drugs from zero-order release systems using in-vitro data, it is important to choose a model that closely approximates the conditions in the GIT (1,2). Ideally, the drug should be released in this model for approximately 8–16 hr. Therefore, it is necessary to test the release of drugs in acid and alkaline pH dissolution media (3,4). To effectively test the in-vitro release from a drug delivery system, it is necessary to first test it in simulated gastric fluid, followed immediately by simulated intestinal fluid (5–8). Ideally, the drug delivery system should release drug at a zero-order rate in both of these simulated fluids for a time similar to the GIT residence time. A new core-in-cup oral drug delivery system that has the ability to release soluble (caffeine) and insoluble (ibuprofen) drugs at a zero-order rate of release in dissolution media has been developed (9). The core-in-cup tablets were manufactured with the aid of a novel adjustable punch that has the ability to produce cup-shaped tablets of various depths (10). Figure 1 is a graphical representation of the core-in-cup tablet used in this study. The purpose of this study was to develop and evaluate the new core-in-cup oral tablet for its dissolution characteristics in a simulated gastrointestinal (GI) medium at a zero-order rate for approximately 8–16 hr

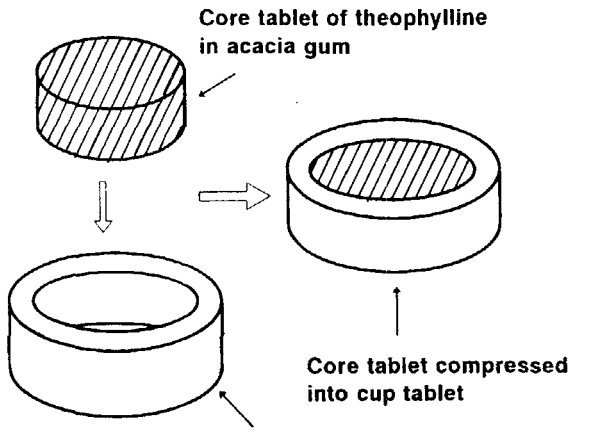


**Figure 1.** Theophylline core-in-cup tablet.

using theophylline (intermediate solubility) as a model drug. In order for the test to be relevant and reproducible, it was decided that it would be best to test the dissolution of theophylline in the presence of sequenced simulated GI fluids in the BP paddle apparatus. The effect the sequenced simulated fluids on the rate of release of theophylline from the core-in-cup tablets was also tested.

The kinetics of dissolution from the core-in-cup tablets were examined to determine how well the dissolution rate fits the Korsmeyer et al. (11) relationship depicted in Eq. (1) below.

$$\frac{M_t}{M_\infty} = k \cdot t^n \tag{1}$$

or,

$$\log \frac{M_t}{M_\infty} = \log k + n \log t \tag{2}$$

where $M_t/M_\infty$ is the fractional dissolution of the drug, $t$ is the dissolution time, k is a constant incorporating structural and geometric characteristics of the release device, and $n$ is the time exponent indicative of the mechanism of dissolution. For example, $n = 0.5$ for square root of time kinetics and $n = 1.0$ for zero-order kinetics.

This classification has been successfully used by Ford et al. (12) to characterize the release of a number of different drugs from HPMC matrices. This relationship is just as applicable to the rate of dissolution as it is to the rate of release, because it is the rate of release that determines the rate of dissolution in controlled-release preparations. When the logarithm of the fraction in solution is plotted versus the logarithm of time in minutes, the slope of the graph will give one the value of the $n$ exponent. In order for Eq. (2) to be applicable, the intercept of the graph must pass through the origin, i.e., log k must be zero. This correction to data can be achieved by correcting the sampling time data of cumulative fraction in solution versus the square root of time. The sampling times are then corrected by linear regression so that the graph passes through the origin (12).

## 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, St. Louis, MO) were ground in a mortar and the fraction passing through a no. 150 standard UK sieve was used.

Pancreatin from porcine pancreas with an activity at least equal to USP specifications, and pepsin from porcine stomach mucosa with 550 units/mg activity were obtained from Sigma Chemical Company and were used as supplied. 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.

## METHODS

### Formulations

Granules of 10% w/w, 20% w/w, and 30% w/w, acacia with theophylline were made using 45% v/v aqueous ethanol as granulating agent. The powders were mixed in a mortar to a homogenous mass and then passed through an Erweka AGS granulator fitted with a 500 μm stainless steel perforated screen. Once the granules were dried in the oven, 0.1% w/w magnesium stearate was added as lubricant. Flat disk-shaped core tablets of 7 mm diameter and 5 mm thickness were then compressed on a Manesty F3 single punch tabletting press. The hardness of the core tablets was first measured on a Pharma Test PTB 311 hardness tester. The press was then adjusted to produce core tablets of approximate hardness of 40 $N/m^2$ and thickness of 5 mm. The average weights of the core tablets and their standard deviations for each formulation are listed in Table 1. The theophyline cores were then compressed together with the 10% w/w carnauba wax in ethylcellulose cups to a depth of 4 mm as described previously (10).

### Dissolution Studies

The BP 1988 paddle method was utilized in all of the dissolution studies. Dissolution rates of the tablets were monitored using a Caleva model 7ST dissolution tester. A 1000-ml volume of freshly prepared simulated gastric fluid TS USP XX was used as the dissolution medium during the first 2 hr, and then was replaced by 1000 ml of freshly prepared simulated intestinal fluid TS USP XX for an additional 10 hr. At time zero, a core-in-cup tablet was placed in the simulated gastric fluid equilibrated at 37°C ± 0.5°C. After 2 hr, the core-in-cup tablet was then carefully removed from the simulated gastric fluid and placed in simulated intestinal fluid preheated and equilibrated at 37°C ± 0.5°C for a further 10 hr. All experiments were carried out at 50 rpm. One-milliliter samples were withdrawn from the dissolution media for theophylline determination after various time intervals.

*Table 1*

*Weights of Theophylline Core Formulations*

| % w/w Acacia | Weight of Core (±SD) ($n$ = 10) |
|---|---|
| 10 | 158 (8.367) |
| 20 | 171 (10.035) |
| 30 | 182 (11.612) |

### Theophylline Analysis

Samples withdrawn from the dissolution media were first centrifuged for 20 min at 12,000 rpm to remove the turbidity from the pancreatin and other insoluble particles. A ~200 μl aliquot of the clear supernatant was added to 200 μl of 0.02% w/v caffeine is distilled water, which served as an internal standard.

Theophylline/internal standard ratios in the 400 μl solutions were analyzed using 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 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 was based on comparison to standard solution curves.

## RESULTS AND DISCUSSION

The dissolution of theophylline from the core-in-cup tablets was consistent in both simulated fluids. Figure 2 graphically describes the dissolution of theophylline from the core-in-cup tablets over an 8-hr period.

The theophylline was released and dissolved from the core-in-cup tablets at a rate that was more consistent (as verified by an LSD analysis of variance test) with a zero-order dissolution rate than a first-order dissolution

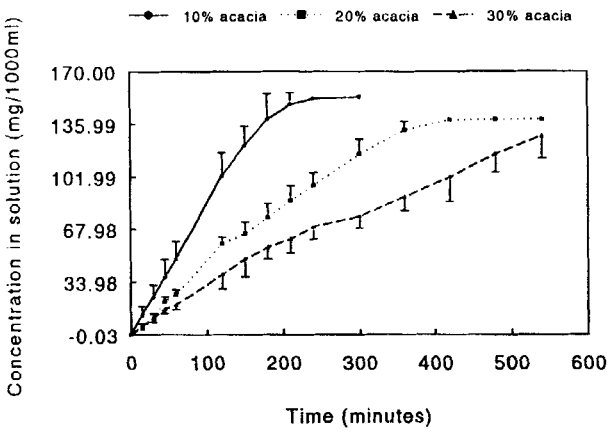


**Figure 2.** Dissolution of theophylline from core-in-cup tablets in simulated gastrointestinal fluids.

rate in both simulated gastric and intestinal fluids. Dissolution rates and the corresponding correlation coefficients of the dissolution of theophylline for zero-order and first-order dissolution models from the various simulated fluids are listed in Table 2. Dissolution of theophylline in the simulated gastric fluid TS is at a slightly higher rate than in simulated intestinal fluid TS. The dissolution rates (based on zero-order dissolution) of theophylline from the 10%, 20%, and 30% acacia core-in-cup tablets were 0.87 mg/min, 0.53 mg/min, and 0.27 mg/min, respectively in simulated gastric fluid TS, and 0.61 mg/min, 0.30 mg/min, and 0.20 mg/min, respectively in simulated intestinal fluid TS. This is probably because theophylline is slightly more soluble in acidic medium than it is in alkaline medium. This increase in the solubility of the embedded theophylline in the acacia makes the core portion of the tablet erode at a slightly increased rate. The increased erosion rate then leads to an increase in the release of theophylline with a resultant increase in the rate of dissolution. Since the release of theophylline from the core-in-cup tablet is slower than the rate of dissolution, it appears that the rate of release is the rate-controlling step. Therefore, this core-in-cup system is a good sytem for zero-order release of theophylline.

***Table 2***

*Dissolution Model Exponents, Correlation Coefficients, and Dissolution Rates of Theophylline in Various Simulated Media*

| Acacia % | Order of Model Used | Correlation Coefficient (±SD) ($n$ = 3) | $n$ for Best Model (±SD) ($n$ = 3) | Rate of Dissolution (±SD) ($n$ = 3) |
|---|---|---|---|---|
| Simulated gastric fluid TS | | | | |
| 10 | Zero | 0.998 (0.002) | 0.973 (0.052) | 0.874 (0.096) |
| | First | 0.980 (0.008) | | |
| 20 | Zero | 0.996 (0.002) | 1.047 (0.046) | 0.526 (0.093) |
| | First | 0.970 (0.009) | | |
| 30 | Zero | 0.997 (0.002) | 1.033 (0.020) | 0.269 (0.028) |
| | First | 0.969 (0.015) | | |
| Simulated intestinal fluid TS | | | | |
| 10 | Zero | 0.989 (0.009) | 1.008 (0.024) | 0.611 (0.102) |
| | First | 0.986 (0.012) | | |
| 20 | Zero | 0.993 (0.006) | 1.033 (0.032) | 0.300 (0.029) |
| | First | 0.970 (0.018) | | |
| 30 | Zero | 0.984 (0.016) | 1.021 (0.028) | 0.204 (0.022) |
| | First | 0.948 (0.029) | | |
| Simulated gastric and intestinal fluid TS | | | | |
| 10 | Zero | 0.996 (0.002) | 1.026 (0.027) | 0.701 (0.193) |
| | First | 0.970 (0.002) | | |
| 20 | Zero | 0.992 (0.007) | 1.150 (0.098) | 0.388 (0.042) |
| | First | 0.972 (0.004) | | |
| 30 | Zero | 0.987 (0.012) | 1.161 (0.065) | 0.224 (0.027) |
| | First | 0.907 (0.010) | | |

Acacia does not seem to have any effect on the zero-order rate of dissolution. All three concentrations of acacia tested released theophylline at a zero-order rate of release. However, the ability to release theophylline at a zero-order rate for a prolonged period of time is dependent on the concentration of acacia used.

For a theophylline concentration of 100 mg in the core of the tablet, the rate of release over a period of 12 hr will have to be 0.1389 mg/min. Therefore, the optimal concentration of acacia can be calculated by substituting this rate (the rate that releases drug over a period of 12 hr) into Eq. (3) and then solving for the concentration of acacia needed. Eq. (3) was obtained from the linear regression of the zero-order dissolution rates versus concentration of acacia used in the core-in-cup tablets to produce those rates. The square of the correlation coefficient for this linear relationship was 0.9688.

$$C = 37.7842 - 40.6217 \cdot R \quad (3)$$

where, $R$ is the zero-order release rate (from overall dissolution data) of theophylline from core-in-cup tablets in mg/min; and $C$ is percent w/w concentration of acacia.

Solving Eq. (3) then gives a value of 32.14 for the percent w/w acacia to add to the theophylline to release theophylline at a rate of 0.1389 mg/min in simulated gastric fluid TS for 2 hr followed by simulated intestinal fluid TS for 10 hr.

These results indicate that the new core-in-cup system has the ability to release theophylline at zero-order rate of release in simulated GI fluids for varying predetermined periods of time depending on the amount of acacia used. There is a linear relationship between the acacia concentration and release rate. A concentration of approximately 37% w/w of acacia in 100 mg theophyline should be released at a zero-order rate in vivo for a period of approximately 12 hr.

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