Drug Development and Industrial Pharmacy, 26(7), 767–772 (2000)

COMMUNICATION

Optimization and Development of a Core-in-Cup Tablet for Modulated Release of Theophylline in Simulated Gastrointestinal Fluids

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ABSTRACT

A triple-layer core-in-cup tablet that can release theophylline in simulated gastrointestinal (GI) fluids at three distinct rates has been developed. The first layer is an immediate-release layer; the second layer is a sustained-release layer; and the last layer is a boost layer, which was designed to coincide with a higher nocturnal dose of theophylline. The study consisted of two stages. The first stage optimized the sustained-release layer of the tablet to release theophylline over a period of 12 hr. Results from this stage indicated that 30% w/w acacia gum was the best polymer and concentration to use when compressed to a hardness of 50 N/m^2. The second stage of the study involved the investigation of the final triple-layer core-in-cup tablet to release theophylline at three different rates in simulated GI fluids. The triple-layer modulated core-in-cup tablet successfully released drug in simulated fluids at an initial rate of 40 mg/min, followed by a rate of 0.4085 mg/min, in simulated gastric fluid TS, 0.1860 mg/min in simulated intestinal fluid TS, and finally by a boosted rate of 0.6952 mg/min.

Key Words: *Dissolution; Modulated release; Nocturnal asthma; Tableting.*

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INTRODUCTION

Constant blood levels of drugs used to treat various diseases are not always a desirable objective of drug formulation. There are many cases for which a variable controlled level of drug is preferred (1–3). To achieve a variable, yet controlled, blood level of drug, the release from the drug delivery system must be modulated to suit the required blood levels for effective treatment. This, of course, has led to the development of modular, pulsatile, and/or variable controlled-release drug delivery systems. Although the parenteral route of delivery has been widely investigated (4–6), oral drug delivery systems are scarce. Those oral systems that have been investigated include modulated drug release mainly via pH variability (7), erosion of laminates of polymer and drug (8,9), or a combination of both (10). Erosion of drug-loaded laminates does not release drug in a sequential way, but rather in a sigmoidal release pattern. It is very difficult to regulate the erosion of each layer; as a result, all layers start eroding at the same time. The systems that utilize pH as their mechanism of controlling the release of drug are solely dependent on the pH of the gastrointestinal (GI) tract and are therefore not very flexible in their release pattern.

The core-in-cup modulated-release tablet developed in this study released different concentrations of drug in strict sequence and was not dependent on the pH of the GI tract. To demonstrate the usefulness and flexibility of this drug delivery system, a once-daily, oral, core-in-cup tablet that modulates a triphasic release of theophylline was developed and tested. The tablet was designed to release theophylline at rates that are in line with its chronopharmacokinetic requirements. Higher theophylline levels are desired in the early hours of the morning; therefore, higher nocturnal levels are required to treat nocturnal asthma. With this in mind, a once-daily core-in-cup tablet with an immediate-release layer, a sustained-release layer, and a late nocturnal booster layer was formulated as shown in Fig. 1. The sustained-release layer was designed to release at a zero-order rate over a period of 12 hr before the nocturnal boost was released. The type of erodible polymer, its concentration, and the hardness of compression of the sustained-release layer were investigated to optimize the release of theophylline at a zero-order rate over the 12-hr period.

MATERIALS

Acacia and polyethyleneglycol 6000 (PEG6000) were supplied by Saarchem (Pty) Limited, South Africa. The acacia and PEG6000 had viscosities of 53 cps and 43 cps, respectively, as 4% aqueous solutions at 23°C. Hydroxypropylmethylcellulose (HPMC) K4M premium EP was supplied by Colorcon Limited, England. HPMC K4M has a viscosity of 3500–5600 cP as a 2% solution in water at 20°C. The HPMC had already been screened through a no. 40 standard U.S. sieve. 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 U.K. 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 and were used as supplied. Ethylcellulose (Riedel de-Haën, South Africa) and carnauba wax (Sigma) were also used as supplied. All other reagents used were standard laboratory grade.

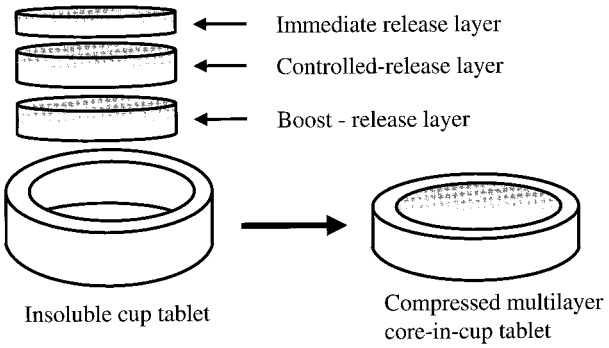

Figure 1. Schematic diagram of modulated-release core-in-cup tablet.

METHODS

Study Design

The study consisted of two stages. In the first stage, the design of a sustained-release core tablet with the ability to release theophylline over a 12-hr period was investigated. A 3×3^2 factorial design was used to determine the level of the independent variables that could produce a zero-order release for about 12 hours. Table 1 shows

Table 1

Levels of Independent Variables

Variable	Factor Level			Units
Concentration of polymer in core	5	10	15	% w/w
Hardness of compressed core	10	30	50	N/m^2

the levels of the independent variables used to optimize the sustained-release layer of the core-in-cup tablet. Once this layer was optimized, the second stage consisted of preparing a triple-layer core-in-cup tablet, which was tested in simulated GI fluids to assess its suitability as a modulated-release tablet for treatment of nocturnal asthma.

Optimization of Sustained-Release Layer

To determine the optimal polymer type, concentration of polymer, and hardness of compression for the sustained-release core of the tablet, theophylline core-in-cup tablets for each polymer of compositions listed in Table 2 were compressed. The method of compression using a novel adjustable inner rod punch and flat punch system has been previously described (11). The zero-order release rate from the tablets was then determined in phosphate buffer (pH 7.5) using a BP paddle dissolution apparatus connected to a UV spectrophotometer via a flow-through cell (12).

Evaluation of Modulated Core-in-Cup Tablet in Simulated Fluids

Once the optimal formula and compression variables for the sustained-release layer were determined, the core-in-cup tablets listed in Table 3 were prepared and tested. To simulate the proportions of theophylline that might be needed in each layer that would mimic the levels required physiologically, it was decided that the quantity of theophylline in the immediate, sustained, and boost layers should be in the ratio of 4:6:5. This was based on a half-life of theophylline of approximately 7–9 hr.

The BP 1988 paddle method was utilized in all the dissolution studies. Dissolution rates of the tablets were monitored using a Caleva model 7ST dissolution tester (Dorset, UK). A volume of 1000 ml of freshly prepared simulated gastric fluid test solution (TS) USP 20 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 20 for an additional 12 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 an additional 12 hr. All experiments were carried out at 50 rpm. Samples were centrifuged and analyzed by high-performance liquid chromatography (HPLC) using caffeine as an internal standard.

Theophylline Analysis from Simulated Fluids

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 in distilled water, which served as an internal standard. Theophylline/internal standard ratios in the 400-μl solutions were analyzed using a 30-cm Beckman ultrasphere ODS 5-μ column connected to a Beckman System Gold HPLC consisting of

Table 2

*Release Rate of Theophylline from Acacia, PEG6000, and HPMC K4M (*c, *% w/w;* h, *hardness N/m*^{2})

			Theophylline Release Rate (mg/min)		
Run	*h*	*c*	Acacia	PEG6000	HPMC K4M
1	10	5	0.4593	0.5745	0.0972
2	10	10	0.4166	0.4456	0.0877
3	10	15	0.3686	0.5064	0.0672
4	30	5	0.4534	0.5558	0.0773
5_a	30	10	0.4691	0.5107	0.0711
5_b	30	10	0.4117	0.5386	0.0701
6	30	15	0.3322	0.4221	0.0589
7	50	5	0.3974	0.5099	0.0834
8	50	10	0.3614	0.4635	0.0742
9	50	15	0.2786	0.3964	0.0587

Table 3

Composition of the Modulated Core-in-Cup Tablet Layers

Ingredient	Concentration (mg)	Thickness (mm)
Immediate-release layer		
Theophylline	80	
Sodium starch glycollate	4.5	1
Magnesium stearate	0.5	
Sustained-release layer		
Theophylline	120	
Acacia	53	2.9
Magnesium stearate	1.5	
Boost layer		
Theophylline	100	
Tragacanth	10	
Magnesium stearate	1.5	2.1
Cup tablet		
Ethylcellulose	290	
Carnauba wax	290	

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 and 5% v/v propan-2-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.

Statistical Analysis

Analysis of variance was performed on the data presented in Table 2 using Statgraphics, version 5 (Statistical Graphics Corporation, Englewood Cliffs, NJ). The independent variables were percentage polymer in the core tablet c and hardness of the core tablet h, while the dependent variable was the zero-order rate release (mg/min) from the core-in-cup tablets. Response-surface plots were constructed for the above variables to determine the optimal combination of the variables. Main effects and significant interactions were also calculated. Simple regression models for the two independent variables were also developed from the results as follows:

$$Y_1(c,h) = a_0 + a_1c + a_2h + a_3ch + a_4c^2 + a_5h^2 \quad (1)$$

where $a_0, \ldots, a_5$ are the coefficients of the system, and c and h denote the percentage polymer in the core tablet and hardness of the core tablets, respectively.

Each term in the final regression equation for the release rate was only included if the t test p value was less than .05. The regression coefficients for the effects that were considered insignificant were eliminated, and the model was reestimated. All statistical analysis was performed using Statgraphics, version 5.

RESULTS

Optimization of Sustained-Release Layer

Figure 2 shows the response surface plots of the estimated effects of the independent variables on the rate of release of theophylline from the three polymers used.

Table 4 lists the relevant statistical parameters calculated from the optimization study and consequently used to calculate the optimum polymer and concentration to use for the sustained-release layer of the tablet. Using the calculated reestimated regression coefficients, the percentages w/w for each polymer that can release 120 mg of theophylline over a period of 14 hr (0.1429 mg/min) when compressed to a hardness of 50 N/m^2 was 42%, 29%, and −55% for PEG6000, acacia gum, and HPMC K4M, respectively. When compressed to a hardness of 10 N/m^2, the concentrations that released 0.1429 mg/min were 42%, 36%, and −27% for PEG6000, acacia gum, and HPMC K4M, respectively. The concentration of PEG 6000 was deemed too high to use as there was a 3-mm limitation to the thickness of the sustained-release core in the core-in-cup tablet. Since hardness of compres-

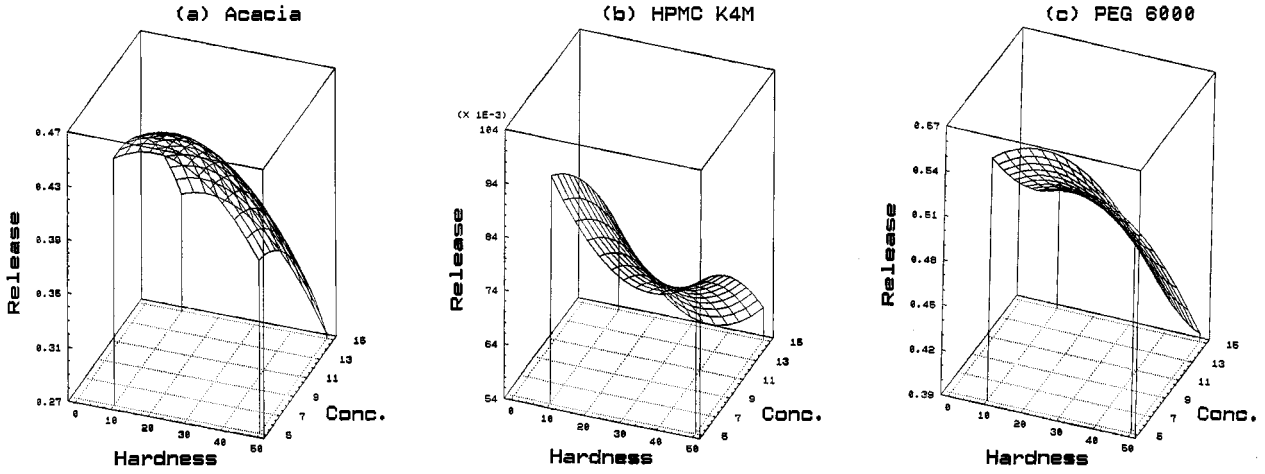

Figure 2. Response surface plots (quadratic function) of estimated effects of *c* and *h* on the rate of release of theophylline from (a) acacia, (b) HPMC K4M, and (c) PEG6000.

Table 4

Relevant Statistical Parameters from Factorial Design

Source	Estimated Effects ± SE	*p*	Regression Coefficient	Regression Coefficient Reestimated
Acacia				
Average constant	0.431 ± 0.015			
			0.389	0.557
c	−0.110 ± 0.021	.006	0.013	−0.011
h	−0.069 ± 0.021	.029	0.004	−0.002
ch	−0.014 ± 0.025	.614	−0.000	
cc	−0.056 ± 0.033	.168	−0.001	
hh	−0.063 ± 0.033	.129	−0.000	
PEG6000				
Average constant	0.502 ± 0.027			
			0.590	0.598
c	−0.105 ± 0.037	.046	−0.014	−0.011
h	−0.052 ± 0.037	.230	0.004	
ch	−0.023 ± 0.045	.647	−0.000	
cc	0.018 ± 0.059	.783	0.000	
hh	−0.051 ± 0.059	.445	−0.000	
HPMC K4M				
Average constant	0.071 ± 0.002			
			0.115	0.122
c	−0.024 ± 0.002	.000	0.000	−0.002
h	−0.012 ± 0.002	.006	−0.002	−0.002
ch	0.003 ± 0.003	.404	0.000	
cc	−0.007 ± 0.004	.124	−0.00	
hh	0.019 ± 0.004	.007	0.000	0.000

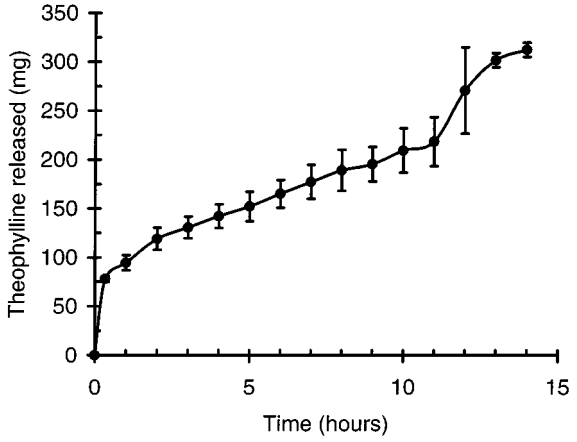

Figure 3. Release of theophylline from the modulated-release core-in-cup tablet in simulated GI fluids.

sion had no significant effect on the release of theophylline from the PEG6000, one could compress the core tablet into a harder tablet. There is, however, a limit to the hardness of 60 N/m^2 that prohibits the tablet from being compressed further when the cores are compressed together with the cup of the tablet. For the core to adhere to the cup portion of the tablet, it must have the ability to be recompressed. It is also not possible to use a low enough concentration of HPMC K4M to achieve a rate of release of 0.1429 mg/min. As a result, 30% w/w acacia, with the core tablet compressed to 50 N/m^2, was used to evaluate the release in the simulated GI fluids.

Evaluation of Modulated Core-in-Cup Tablet in Simulated Fluids

Figure 3 is a plot of amount of theophylline released from the modulated core-in-cup tablets versus time in simulated GI fluids. The triple-layer modulated core-in-cup tablet successfully released drug in simulated fluids at an initial rate of 40 mg/min, followed by a rate of 0.4085 mg/min in simulated gastric fluid TS, 0.1860 mg/min in simulated intestinal fluid TS, and last followed by a boosted rate of 0.6952 mg/min.

Consequently, the core-in-cup tablet developed during this research is a useful drug delivery system that can modulate the release of theophylline at a rate that would be required to match its chronotherapeutics. By means of choosing different erodible polymers of varying concentrations and compressing the core tablets to various hardnesses, it should be possible to produce myriad oral modulated-release tablets. It should also be possible to target the release of drug to various areas in the GI tract by alternating inactive core tablet spacers between core tablet layers of active drug(s). The possibility of these systems will be investigated in further research. Another benefit of the system is that the sustained-release layer is released at a zero-order rate.

ACKNOWLEDGMENT

I thank the H. E. Griffin Charitable Trust for financial support during this study.

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