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RESEARCH PAPER

Controlled-Release Hydrophilic Tablets for Individualized Theophylline Therapy

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ABSTRACT

*Directly compressible controlled-release (CR) theophylline tablet formulations with a non-zero-order drug release were prepared using various grades of Methocels®. These tablet formulations were employed in the individualization of therapy with the aid of a pharmacokinetic simulation model developed with STELLA® II computer software. In vitro drug release data were used to simulate plasma concentration-time (*C,t*) profiles based on a wide range of previously reported patient pharmacokinetic parameters (clearances of 2–5 L/hr and apparent volumes of distribution of 20–50 L). The simulations indicated that formulations containing low-viscosity Methocels (E4, K4, and K4CR) were suitable for individualizing theophylline therapy. Average steady-state concentrations were well within the therapeutic range of 10–20 μg/ml. High-viscosity polymers such as E10CR, K15, and K15CR yielded subtherapeutic concentrations and were deemed unsuitable. Thus, a pharmacokinetic simulation program capable of predicting in vivo* C,t *profiles (even though theophylline release occurred by a non-zero order) may be useful for individualizing theophylline therapy that involves CR formulations.*

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INTRODUCTION

The bronchodilating effect of theophylline is closely related to the plasma concentration of the drug. The therapeutic range of this drug is rather small, between 10 and 20 μg/ml of plasma concentration. Approximately 90% of the dose is biotransformed by microsomal oxidative enzymes, and the remaining dose is excreted unchanged in the urine (1). Due to the extensive metabolism of this drug, the genetic, environmental, pathophysiological, and pharmacokinetic factors that affect biotransformation rates make its dosage highly unpredictable (1). Therefore, individualization of the therapy has been accepted as the rational approach in achieving optimal effect (2).

Controlled release (CR) theophylline formulations offer several advantages over conventional rapid-release formulations, such as decreased fluctuations in the plasma concentrations, around-the-clock stabilization of the hyperreactive airways, and increased patient compliance as a result of decreased frequency of dosing (3). Although the use of CR formulations has been increasing steadily, such formulations offer potential difficulty in the individualization of theophylline therapy. This is due to the differences in drug release of currently marketed slow-release products (3–5). Although several methods and algorithms have been developed to aid in the individualization of therapy, many of them are limited to the intravenous administration route (2,6,7) or assume a constant-release rate (zero order) of the drug from the dosage form (3,8). Therefore, such methods cannot be implemented in most cases involving CR formulations for which the release rate changes with time. In this pilot study, cost-effective theophylline CR tablets with identical formulation parameters but offering different drug release rates were prepared to make them suitable for individualized therapy. An easy-to-use pharmacokinetic simulation model in which in vitro drug release–time data and individual patient's apparent volume of distribution and clearance values were utilized as the input. The individual patient pharmacokinetic parameters, rather than population-based values, were utilized in the selection of appropriate formulations and dosing regimens.

MATERIALS

Hydroxypropyl methylcellulose (HPMC) ethers—Methocel™ E4CR, E4, K4CR, K4, E10CR, K15CR, and K15—were supplied by Dow Chemical Company of Michigan. Anhydrous theophylline (BASF Fine Chemicals, NJ) and microcrystalline cellulose (Avicel™ PH-101, FMC Corporation, DE) were also generously donated. Magnesium stearate was purchased from Nuodex, Incorporated, of Piscataway, New Jersey. Monobasic potassium phosphate, enzyme-grade Tween™ 80, sodium hydroxide, hydrochloric acid, and water of high-performance liquid chromatography (HPLC) grade were used as supplied by Fisher Scientific (Pittsburgh, PA). The STELLA® II (version 2.2.1) simulation program (High Performance Systems, Inc., Lyme, NH) was used on a Macintosh Quadra computer (Apple Computer, Inc., Cupertino, CA).

METHODS

Apparent Viscosity Determination of Methocel Dispersions

Apparent viscosities of different Methocel grades were determined by slightly modifying the previously reported method (9). In a glass beaker, 6 g of the HPMC polymer (accurately weighed) was placed in a glass beaker; 294 g water, previously heated to 80°C–90°C, was added to the HPMC. The dispersion was stirred for about 10 min using a propeller-type mixer and was placed in an ice bath. Stirring continued for about an hour to effect complete dispersion. The weight of the solution was adjusted to 300 g and stirred if necessary. The solution was then allowed to stand at 20°C before the apparent viscosity determination. Apparent viscosity was determined using Brookfield synchrolectic viscometer-RV with either a 3- or 5-numbered spindle at 20 rpm.

Tablet Preparation

The CR tablets were prepared using the following: anhydrous theophylline 300 mg, microcrystalline cellulose (Avicel PH-101) −352.7 mg, as the diluent, Methocel 73.3 mg, as the hydrophilic matrix component and magnesium stearate 7.3 mg, as the lubricant, making the tablet weight 733.3 mg. The immediate-release (IR) tablets (formulation A) were prepared by replacing Methocel with an equal amount of Avicel PH-101. Powder blends (approximately 1.5 kg) were prepared by mixing the weighed amounts of ingredients in a twin-shell blender at approximately 30 rpm for 5 min. The particle size of all the ingredients was less than 250 μm. The compression was carried out on an 18-station rotary press (model HT AP 18SS-U/I, courtesy Elizabeth-Hata, Inc., North Huntingdon, PA) at a speed of 25 rpm using 15/32-inch diameter standard concave punches and appropriate dies. The compression pressure was maintained at approxi-

mately 26,000 lb/inch^2. A total of eight formulations was prepared. Formulations B–E contained Methocel E4CR, E4, K4CR, and K4, respectively, and formulations F–H had E10CR, K15CR, and K15, respectively.

Physical Characteristics of the Powder Blends and Tablets

Angle of Repose

The angle of repose ϕ was determined by a previously reported method (10). Briefly, 5 g of powder blend was placed in a funnel with an orifice that was closed with a plastic plug. The funnel was held in place so that its orifice was 4–5 cm above the bench-top level. The plug was then removed, and powder was allowed to flow freely through the funnel. The radius r and height h of the pile of powder was then measured in triplicate, and the angle of repose was calculated using the following equation:

$$\phi = \text{Arctan}(h/r) \quad (1)$$

Tablet Friability

For tablet friability, 20 tablets were weighed and then placed in an Erweka friability tester. They were then allowed to fall freely 100 times from a height of 6 inches. The tablets were then dedusted, and any loss in weight due to fracture or abrasion was recorded as percentage weight loss.

Tablet Dimensions and Hardness

Tablet diameter, thickness, and hardness of 10 randomly selected tablets per batch were determined using PharmaTest™ tablet tester.

Drug Content Analysis

An accurately weighed tablet was crushed to powder. About 100 mg of this powder was accurately weighed, placed in a volumetric flask, and diluted to 100 ml with distilled water. The content was stirred using a magnetic stirrer for 1 hr at room temperature. A 3-ml aliquot was filtered through a 0.45-μm filter and analyzed spectrophotometrically at 271 nm to determine the amount of theophylline. This analysis was conducted in triplicate.

In Vitro Dissolution Studies

The in vitro dissolution studies were performed in simulated intestinal fluid (pH = 7.4) using a USP type II apparatus at a paddle speed of 100 ± 1 rpm and a temperature of 37°C ± 1°C. Samples (1 ml) were withdrawn at predetermined time intervals, filtered through a 0.45-μm nylon filter, diluted, and assayed at 271 nm using a Perkin-Elmer ultraviolet visible (UV/Vis) spectrophotometer, model 124.

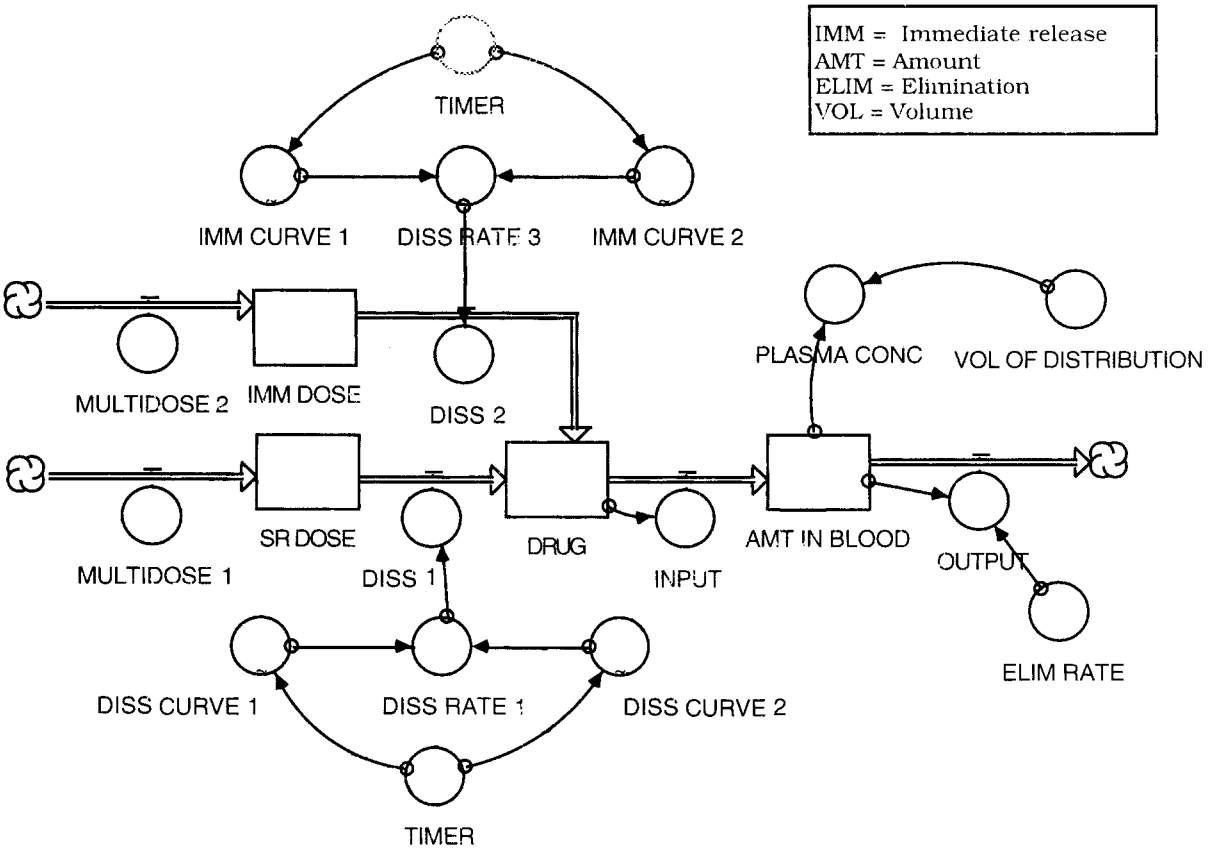
Simulation Model

A one-compartment open model of peroral theophylline kinetics was constructed using the STELLA II program (Scheme 1). This model was selected since, although a two-compartment model has often been used, the distribution phase of theophylline is quite rapid and is completed within 30 to 45 min. Therefore, for most situations, a one-compartment open model is adequate (11). The reader is advised to refer to previously published comprehensive reports (12–15) to gain more knowledge about the utility of the STELLA simulation program for pharmacokinetic simulations.

The simulations, based on the Runge-Kutta algorithm, were performed using a short simulation interval dt of 1 min for accurate results. Since the rate of in vitro release was not constant, this rate (amount released/dt) was calculated every minute for each 12-hr dissolution profile. The same in vitro cumulative percentage drug release–time data was fed into the simulation model via flow regulators, diss curve 1 and 2. Diss curve 2 was started 1 dt after diss curve 1. The difference in the amount released, calculated by diss curves 1 and 2, gave the amount released per dt at that time. In other words, that was the rate of release for that instant. Therefore, the smaller the dt was, the more accurate the calculations were. The calculations of the pharmacokinetic parameters used for simulations are explained below. The equations required to construct the simulation model (Scheme 1) are listed in Appendix 1. To predict the steady-state plasma concentrations of the drug, a pulse function, denoted ''MULTIDOSE'' in the scheme, was used in the simulation model. This function generated a pulse input of specified size (dose) set to fire initially at time $t = 0$ and then to repeat at every specified time interval (e.g., $t = 720$ min).

Calculations of Pharmacokinetic Parameters

In an extensive study involving 200 patients, Jusko et al. (1) reported the effect of various factors (e.g., age; consumption of tobacco, alcohol, or marijuana; existence of concurrent disorders; obesity; etc.) on patients' theophylline clearance values. For the simulation model, we selected a range of pharmacokinetic parameters: clear-



Scheme 1. Pharmacokinetic simulation model of in vivo theophylline disposition following multiple dosing.

ance *Cl* of 2.0, 3.5, and 5.0 L/hr, and apparent volume of distribution V_d of 20, 35, and 50, which encompassed most of the patient population as reported[1] by Jusko et al. (1) and Slotfeldt et al. (16). Heavy alcohol consumption and cirrhosis of the liver are, reportedly, the two major factors contributing to low *Cl* and high V_d values. On the other hand, low V_d and high *Cl* conditions may be encountered in young adults who use tobacco or marijuana (1). For a detailed discussion of the relationship of *Cl* and V_d to pathophysiological conditions, the reader is referred to an invaluable study reported by Jusko et al. (1).

For this study, a range of pharmacokinetic parameters encountered as a result of various pathophysiological conditions was used to generate a Latin square design as shown in Table 1 (1,16). The cells containing $Cl = 3.5$ and 5 L/hr and $V_d = 20$ L were not included in this Latin square design (Table 1) because of their unacceptably high elimination rate constants K_{el}. Using the in vitro release data of the tablets in the above model, simulations were performed employing these pharmacokinetic parameters (Table 1) for multiple dosing. The steady-state condition was considered to have been reached when the

[1] Clearance values reported as L/hr/kg were converted to L/hr using average patient body weights (17).

Table 1

Latin Square Design of Pharmacokinetic Parameters[a] Used for Simulations

Clearance (L/hr)	Apparent Volume of Distribution (L)		
	20	35	50
2.0	0.100	0.057	0.040
3.5	0.175	0.100	0.070
5.0	0.250	0.140	0.100

[a] Elimination rate constants (hr^{-1}) given in individual cells were calculated as follows: $K_{el} = Cl/V_d$

dose-to-dose variability of respective maximum and minimum concentration values was less than 0.01 μg/ml. The steady-state concentrations C^{ss}_{upper} and C^{ss}_{lower} were obtained as the output of the simulation model. The average steady-state concentration C^{ss}_{ave} was calculated as follows:

$$C^{ss}_{ave} = \left(C^{ss}_{upper} - C^{ss}_{lower}\right) \Big/ \left(\ln \frac{C^{ss}_{upper}}{C^{ss}_{lower}}\right) \quad (2)$$

RESULTS AND DISCUSSION

Physical Properties of Powder Blends and Tablets

The angles of repose of the powder blends or formulations containing different grades of Methocel were comparable (Table 2). The flowability of these formulations was also found to be adequate (18). The tablets compressed on a rotary tablet press exhibited very low friability and acceptable uniformity in compression weight (19). The physical characteristics of the tablets are presented in Table 3. As shown, the tablet hardness was greater than 25 kiloponds due to the high compression pressure. Despite the high compression pressure, the tableting machine was highly operable. All the other parameters were within limits.

In Vitro Dissolution Studies

The drug release profiles were characterized by an initial burst effect with a greater amount of drug released, followed by a more-uniform release of the drug (Fig. 1). Such a biphasic release is often observed from hydrophilic matrix systems (20,21). In the initial phase, the drug release was possibly due to the dissolution of free drug on the surface of the matrix and erosion. In the second phase, a linear relationship of the drug release to the square root of time was observed from all the formulations, suggesting a diffusion-controlled mechanism of drug release. As the release-rate-limiting polymer changes from a glassy state to a rubbery state, a gel structure is formed around the tablet matrix, which considerably decreases the release of the drug since the drug has to diffuse through this gel barrier into the bulk phase. The strength of the gel depends on the chemical structure and molecular size of the polymer. Generally, a direct dependence was observed between the time taken to release 50% (T_{50}) and the apparent viscosity of the polymer used in the tablet (Fig. 2). Specifically, K4 polymers (K4 and K4CR) yielded greater T_{50} values than E4 polymers (E4 and E4CR) despite comparable viscosities. It is known that K series polymers are faster-hydrating polymers and therefore are capable of forming a gel structure faster than the E series polymers (22).

Table 2

Angles of Repose of Formulations Containing Different Grades of Methocels

Formulation	Methocel Type	Angle of Repose (Degrees)
A	—	30.57
B	E4CR	32.93
C	E4	30.03
D	K4CR	33.29
E	K4	31.62
F	E10CR	33.70
G	K15CR	31.90
H	K15	33.46

Individualization of the Therapy

Using the pharmacokinetic parameters given in Table 1 and the in vitro dissolution data, simulated in vivo plasma concentrations–time data that resulted from multiple dosing of selected CR formulations were generated for at least 72 hr (Fig. 3). The pharmacokinetic parameters such as C^{ss}_{ave} and elimination half-life ($T_{1/2}$) of individual cases are reported in Table 4. The values shown are derived from Table 1 and plasma concentration–time data generated from the simulations (Fig. 3). In all the cases, a loading dose of an IR tablet (formulation A) was coadministered with a CR product at time $t = 0$. In the cases for which $Cl = 5.0$ L/hr, $V_d = 50$ L (Fig. 3i) and 35 L (Fig. 3ii); the high elimination rate constants necessitated the use of two IR formulations instead of one at time $t = 0$. Also, the CR formulation containing K4 Methocel (formulation E) and having the fastest in vitro drug release rate in phase II (Fig. 1) was found to be suitable. High values of Cl and V_d may be observed in a select group of overweight young adults (<40 years) who are also smokers (1).

As shown in Figs. 3i and 3ii, for these pharmacokinetic parameters, the simulations indicated that a dosing regimen of three times a day was necessary to maintain the drug concentrations in the therapeutic range. For the rest of the cases studied (Figs. 3iii to 3vii), only a twice-a-day regimen was appropriate. For subjects having $Cl = 3.5$ L/hr and $V_d = 50$ or 35 (Figs. 3iii and 3iv, respectively), a coadministration of one IR tablet was found to be necessary with the CR formulation. The CR

Table 3

Physical Characteristics[a] of the Tablets Containing Different Methocels

Formulation	Thickness (mm)	Diameter (mm)	Hardness (Kp)	Friability (% w/w)	Weight (mg)	Drug Content (mg/tablet)
A	5.42 ± 0.08	11.60 ± 0.02	29.90 ± 1.11	0.33%	732.5 ± 10.0	304.4
B	5.96 ± 0.03	11.90 ± 0.01	25.50 ± 0.96	0.15%	722.5 ± 5.56	300.7
C	5.41 ± 0.06	11.68 ± 0.09	29.34 ± 2.12	0.38%	740.0 ± 6.98	306.3
D	5.92 ± 0.11	11.63 ± 0.05	25.55 ± 6.49	0.28%	750.8 ± 13.0	312.4
E	5.87 ± 0.06	11.62 ± 0.07	28.26 ± 1.89	0.41%	748.0 ± 6.10	306.5
F	5.99 ± 0.03	11.77 ± 0.01	27.60 ± 1.64	0.36%	734.8 ± 7.73	306.1
G	5.81 ± 0.03	11.79 ± 0.10	27.78 ± 0.97	0.61%	749.1 ± 4.00	315.3
H	5.73 ± 0.07	11.61 ± 0.03	27.96 ± 1.26	0.09%	730.0 ± 5.08	303.0

[a] Mean ± SD.

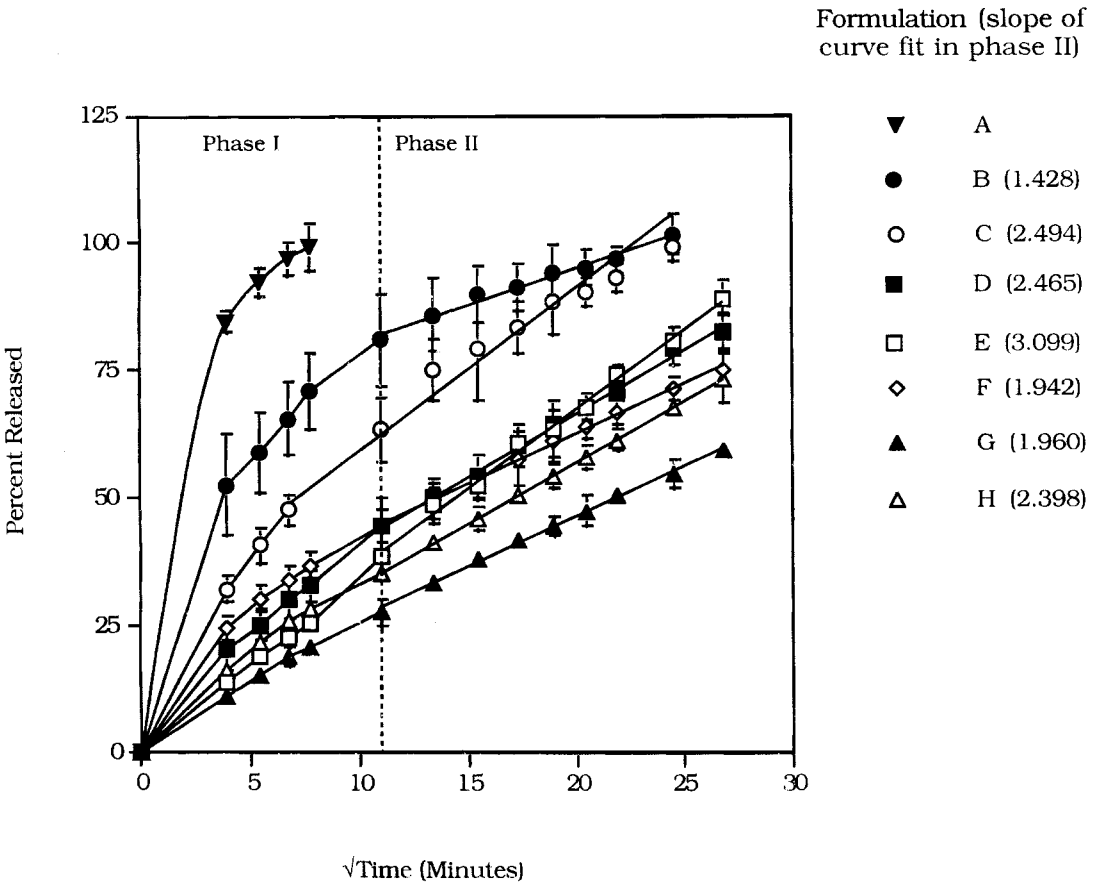


Figure 1. In vitro release of theophylline from hydrophilic matrix tablets in simulated intestinal fluid.

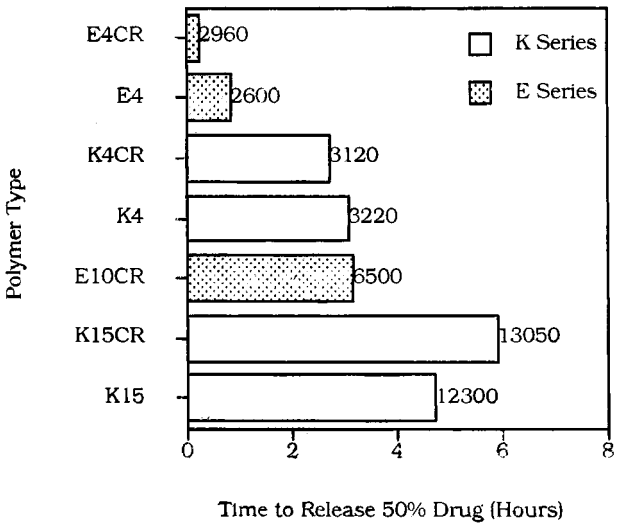


Figure 2. Comparison of the time taken to release 50% drug as a function of the viscosity of methocel used. Apparent viscosity (cps) is reported at the end of each bar.

formulations D and E (containing K4CR and K4, respectively) were used for the respective subjects. Although formulations C and D possess a comparable in vitro drug release rate in phase II, formulation D exhibited less of a burst effect in phase I (Fig. 1). Therefore, it was more suitable in the above case (Cl = 3.5 L/hr, V_d = 50 L). The subjects having lower clearance (2 L/hr) did not require coadministration of an IR formulation, except at time t = 0 (Figs. 3v to 3vii). Among these three subjects, for the one possessing the higher K_{el} of 0.100 hr^{-1} (Cl = 2.0 L/hr, V_d = 20 L) (i.e., Fig. 3vii), formulation E (containing Methocel K4) was more suitable due to its faster release rate in phase II. For the other two cases with lower K_{el} values, the formulation containing Methocel E4 (formulation C) was appropriate. The conditions of reduced clearance, as depicted in Figs. 3v to 3vii (Cl = 2.0 L/hr and V_d = 20 to 50), may be observed in the users of oral contraceptives or in adults (>40 years) who are heavy users of alcohol. Low values of Cl and V_d, as depicted in Fig. 3vii, may be observed in older patients having impaired liver functions or congestive heart conditions (1).

In most of the cases, steady state was reached by administration of four doses. At steady state, the simulated C^{ss}_{ave} were found to be in the therapeutic range. Acceptable values were also obtained for C^{ss}_{upper} and C^{ss}_{lower}.

Overall, the low-viscosity-yielding polymers of the E and K series were found to be more suitable for the formulations studied. Simulations involving formulations F, G, and H (containing Methocels E10CR, K15CR and K15, respectively) yielded subtherapeutic concentrations ($C^{ss}_{ave} \leq 6$ μg/ml) when administered twice or three times a day. Therefore, these formulations were deemed unsuitable for use. Incomplete drug release, as tested in vitro, may be the probable reason for the poor performance of these formulations.

In general, the subjects with a high Cl (≥3.5 L/hr) required more than one 300-mg tablet at every dosing interval. These observations were in concert with those of Laursen, Johannesson, and Weeke (23), who observed that an average daily theophylline dose of 1600 mg was required for patients with a high Cl (average Cl = 4.58 L/hr). Although tablets containing higher drug loading would have been preferable for these patients, the design of the study warranted the use of dosage forms having comparable dimensional characteristics and direct comparisons of dissolution profiles. Therefore, only 300-mg tablets were formulated and utilized for evaluations.

The elimination half-lives for the subjects used in the simulation program varied considerably (from 2.1 to 7.5 hr). This range is representative since a sizeable portion of the patient population has the mean elimination half-life within this limit (1). The hydrophilic matrix tablets developed in this study were found to be appropriate for individualization of therapies of all the subjects, including young subjects in the age group 6 to 19 years, who are known to have higher clearances than adults (1).

Having established the use of the pharmacokinetic simulation model in the individualized therapy, future research involving the in vivo studies of the tablet formulations will aid in predicting the blood concentrations accurately. In such cases, formulation factors such as bioavailability and gastrointestinal transit time can be taken into consideration. Also, the knowledge of patient variables such as food intake, diet, concurrent use of other drugs, and the like may help in further refining the simulation model. Deviations from the simulated plasma concentration profiles may occur due to alteration in the clearance values of the patients, a result of saturable metabolism (24,25) and a circadian rhythm in the clearance (26).

CONCLUSIONS

Hydrophilic matrix tablets containing Methocel as the dissolution-rate-limiting component yielded a biphasic drug release.

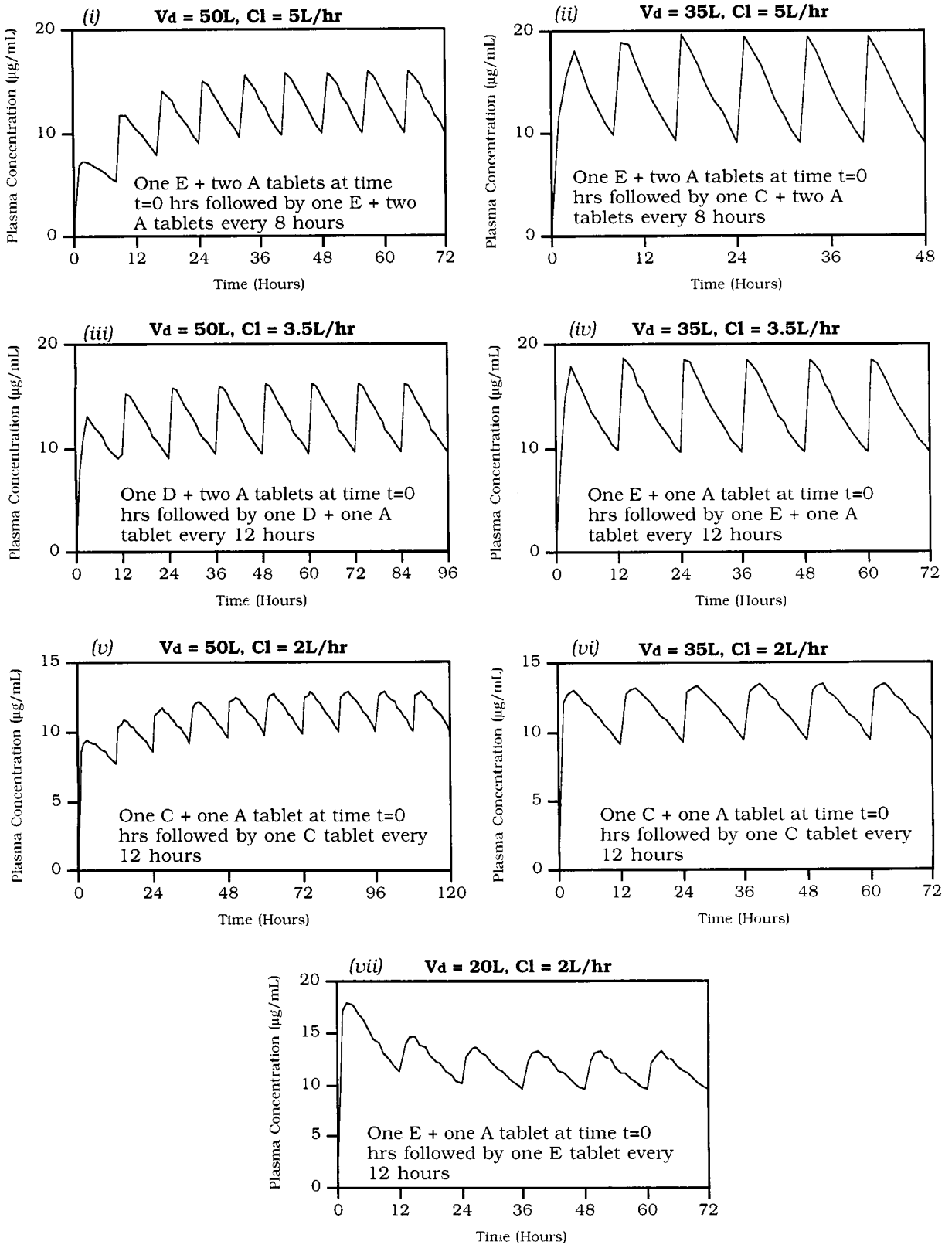


Figure 3. Simulated plasma theophylline concentrations following multiple dosing.

Table 4

Steady-State Pharmacokinetic Data of the Simulations for Individualized Therapy

Methocel Type	Formulation	$T_{1/2}$ (hr)	K_{el} (hr^{-1})	V_d^{ss} (L)	Cl^{ss} (L/hr)	C_{lower}^{ss} (μg/ml)	C_{upper}^{ss} (μg/ml)	C_{ave}^{ss} (μg/ml)
K4	E	3.01	0.100	50	5.0	10.01	15.94	12.75
K4CR	D	4.30	0.070	50	3.5	9.49	16.22	12.56
E4	C	7.53	0.040	50	2.0	9.87	12.69	11.22
K4	E	2.11	0.140	35	5.0	9.04	19.29	13.52
K4	E	3.01	0.100	35	3.5	9.53	18.45	13.50
E4	C	5.27	0.057	35	2.0	9.33	13.40	11.24
E4	E	3.01	0.100	20	2.0	9.47	13.21	11.24

$T_{1/2}$ = elimination half-life computed from steady-state clearance Cl^{ss} and volume of distribution Vd^{ss}; C_{ave}^{ss} = average concentration at steady state calculated from the peak C_{upper}^{ss} and trough C_{lower}^{ss} concentrations at steady state obtained from the simulation runs.

STELLA II software was used to predict pharmacokinetic disposition of various theophylline formulations that exhibited a non-zero order of drug release. In vitro drug release data of the formulations and pharmacokinetic parameters encompassing a wide range of patients were utilized in the simulations to predict steady-state concentrations following multiple dosing with the tablets. The simulations allowed the selection of appropriate formulations and a dosing regimen suitable for individualized therapy.

APPENDIX: EQUATIONS USED TO CONSTRUCT THE SIMULATION MODEL

Amount in blood (t) = Amount in blood ($t - dt$) + (Input − Output) · dt

Initial amount in blood = 0

Drug (t) = Drug ($t - dt$) + (Diss 1 + Diss 2 − Input) · dt

Initial drug = 0

Immediate dose (t) = Immediate dose ($t - dt$) + (Multidose 2 − Diss 2) · dt

Initial immediate dose = 300 mg

Multidose 2 = Pulse (300,0,720) (for every 12-hr regimen)

SR dose (t) = SR dose ($t - dt$) + (Multidose 1 − Diss 1) · dt

Initial SR dose = 0 mg

Multidose 1 = Pulse (300,0,720) (for every 12-hr regimen)

Diss rate 1 = Diss curve 2 − Diss curve 1

Diss rate 3 = Imm curve 2 − Imm curve 1

Diss rate 1 = Diss 1 and Diss rate 3 = Diss 2

Elim rate = 0.00117 min^{-1} (or other elimination rates)

Plasma conc = Amount in blood/volume of distribution

Timer = MOD(Time, 720)

Volume of Distribution = 50 L (or 20, 35, etc.)

Diss curve 1 = Graphical input (% released v/s timer)

Diss curve 2 = Graphical input (% released v/s timer + dt)

Imm curve 1 = Graphical input (% released v/s timer)

Imm curve 2 = Graphical input (% released v/s timer + dt)

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