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Mixture design of theophylline retard formulation

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Summary

Three different cellulose derivatives (hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC) and microcrystalline cellulose (MC)) were used to prepare tablets containing 10% of theophylline with the aid of wet granulation. The retardation effect of different compositions of these cellulose derivatives was investigated. Using mixture design, the formulations with the best retardation properties were selected. On the basis of these results, tablets with different compositions containing 60% (300 mg) of theophylline were prepared. The simulation was performed on a personal computer with the implemented digital simulation language SIMCOS to predict steady-state plasma levels. It was established that formulation C, composed of 34.6% of MC, 4.7% of HPMC, 0.7% of HPC and 60% of theophylline exhibits in vivo the same retardation effect as commercially available theophylline tablets.

Introduction

Theophylline is a well known and very effective drug used in the treatment of acute and chronic asthma. In order to achieve maximum therapeutic benefit with a low risk of severe side effects, the serum concentrations should be maintained within the narrow range of 10–20 mg/l (Dahlquist et al., 1984; Hendeles et al., 1984). Conventional rapid release formulations produce excessive fluctuations in serum concentration, particularly in patients with rapid elimination of the drug (Hendeles et al., 1984). Therefore, sustained release formulations of theophylline are desirable because of its short elimination half-life in humans and to reduce its side effects (Dahlquist et al., 1984). Additionally, a maintenance dosage scheme of 8–12 h is required to avoid large fluctuations in plasma concentrations (Hendeles et al., 1984).

Since most of the commercially available water soluble cellulose derivatives are considered to be stable against microbial attack and safe when ingested orally, it is worthwhile to use them as suitable materials for sustained-release preparations (Nakano et al., 1983).

In the present study we evaluated the retardation effect of some cellulose derivatives (hydroxypropyl cellulose, hydroxypropyl methyl cellulose, and microcrystalline cellulose), when used in dif-

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ferent compositions of tablet formulations. The mixture approach was used for experimental design. An attempt was made to produce tablets with retardation properties similar to those of commercially available theophylline formulations. Using the dissolution results the plasma concentrations of theophylline after single- and multiple-dosage schemes were predicted with the aid of the appropriate pharmacokinetic programs and computer simulation.

Materials and Methods

Theophylline (anhydrous) was supplied by Prodotti Gianni (Italy); hydroxypropylmethylcellulose (HPMC) and hydroxypropyl cellulose (HPC) were purchased from DOW Chemical (U.S.A.). Microcrystalline cellulose (MC) was obtained from FMC Corp. (Ireland). All other chemicals used were of analytical grade.

General concept of mixture design

In the mixture experiments, the restrictions on the levels of each factor are expressed as follows:

$$\sum_{i=1}^{q} X_i = 1 \tag{1}$$

$$0 \leqq U_{ai} \leqq X_i \leqq U_{bi} \leqq 1,\ i = 1, 2, 3, \ldots\ q \tag{2}$$

X_i is the proportion of the i-th component in the mixture where q is the number of components, whereas U_{ai} and U_{bi} are lower and upper bounds on the levels of each component, respectively. Due to the restrictions given in Eqns 1 and 2, the feasible experimental region is the geometrical shape of a convex polyhedron. Extreme vertices, midpoints of edges, centroids of faces and overall centroid are usually taken as primary experimental points. In order to predict response variables, $Y(x)$, the following canonical models can be used by the combination of factors:

$$y(x) = \sum_{i=1}^{q} b_i x_i \tag{3}$$

$$y(x) = \sum_{i=1}^{q} b_i x_i + \sum_{i<j}^{q} b_{ij} x_i x_j \tag{4}$$

$$y(x) = \sum_{i=1}^{q} b_i x_i + \sum_{i<j}^{q} b_{ij} x_i x_j + \sum_{i<j<k}^{q} b_{ijk} x_i x_j x_k \tag{5}$$

b_i, the linear blending value of component i, represents the expected response to the pure component i and b_{ij} is the coefficient of the nonadditive blending of components i and j. The other b_{ijk} are defined similarly. Eqns 3–5 represent linear, quadratic and special cubic models,

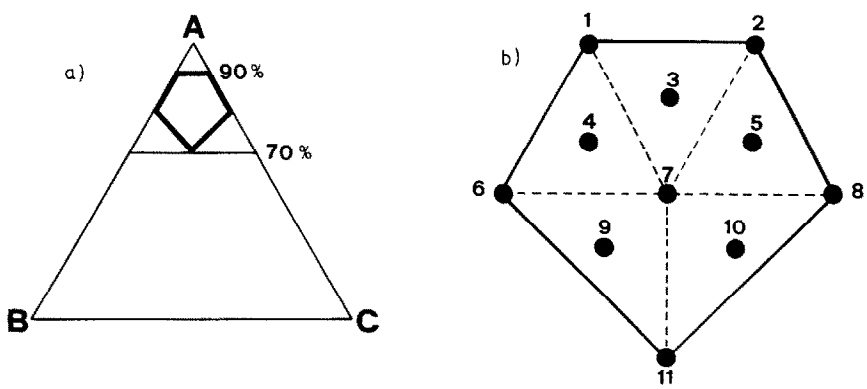

Fig. 1. Definition of the experimental domain by truncation of the three-component initial triangle. (a) Experimental domain in the three-phase diagram; (b) a pentagonal shape of the experimental region with planned experiments.

respectively. The special cubic model is desirable to predict response variables when the interaction term among the factors is thought to be important, even if many experimental points are required to use this model. Calculation of the coefficients is carried out by the least squares method by means of:

$$\boldsymbol{B} = (\boldsymbol{X}'\boldsymbol{X})^{-1}\boldsymbol{X}'\boldsymbol{Y} \quad (6)$$

where $\boldsymbol{B}$ is the vector of the estimates of the coefficients b, $(\boldsymbol{X}'\boldsymbol{X})$ denotes the information matrix and $(\boldsymbol{X}'\boldsymbol{X})^{-1}$, the inverse of $(\boldsymbol{X}'\boldsymbol{X})$, is the dispersion matrix.

Determination of experimental points for granulation

The proportions of HPC (X_1), HPMC (X_2) and MC (X_3) in the three-component mixture were selected as formulation factors. On the basis of preliminary experiments, lower and upper bounds were set as follows:

$$0.10 \leqq X_1 \leqq 0.20$$

$$0.10 \leqq X_2 \leqq 0.20$$

$$0.70 \leqq X_3 \leqq 0.90$$

Within the chosen experimental domain no wet mass adheres to the walls of the mixer bowl.

TABLE 1

Mixture design for the formulation factors

Formulation	Formulation factor (%)		
	MC (X_3)	HPMC (X_2)	HPC (X_1)
1	90	10	0
2	90	0	10
3	87	6.5	6.5
4	83	13.5	3.5
5	83	3.5	13.5
6	80	20	0
7	80	10	10
8	80	0	20
9	77	15	8
10	77	8	15
11	70	15	15

Consequently, the feasible experimental region was a pentagonal shape as shown in Fig. 1.

It was decided to develop a strategy consisting of the division of the experimental domain into four triangles, also called 'simplex-lattices' (Mathien et al., 1983; Cornell, 1990). According to this design, 11 experiments were planned corresponding to the extreme vertices (Expts 1, 2, 6–8, 11) plus the overall centroid points (Expts 3–5, 9, 10).

The experimental design selected is reported in Table 1 and Fig. 1.

Granulation

A Zanchetta Roto J granulator was used for preparation of the granulations. 0.9 kg batches containing MC, HPC, HPMC and theophylline (10%) were mixed at 120 rpm for 10 min. The powder was granulated with water. The binder solution was added by spraying at a flow rate of 50–70 ml/min, a pressure of 4.0 bar and atomized by a pneumatic nozzle of 0.3 mm diameter. The sample was dried in a hot-air oven at 60°C for 4 h. The same procedure was used for the preparation of the granulation containing 60% of theophylline.

Tableting

Tableting was performed on a Korsch EKO single-punch machine (Erweka, Germany), powered by an Erweka AR 400 apparatus. All the granulations were tableted under the same conditions. The upper and lower punches of the tableting machine were adjusted in the following manner: the volume of the cavity for the granulation was 1.1 cm^3 and the thickness of the tablets produced was adjusted to about 0.35 cm, so that the mass of the tablets was about 500 mg.

Dissolution studies

The rotating paddle method was used for determination of the dissolution rate. The apparatus used was the same as that described in USP XXII under Apparatus 2 (Erweka DT-D, Germany). Each tablet was introduced into 1 l of distilled water at 37 ± 0.5°C. Rotation speed of the paddle was adjusted to 100 rpm. 2-ml samples were withdrawn at different time intervals (after

2, 5, 10, 20, 30, 60, 120, 180 and up to 480 min, depending on the dissolution of the formulation tested) and filtered to remove solid particles. The concentrations of the released drug were determined by UV-Vis spectrophotometer (Perkin-Elmer, Lambda 15, Germany) at 271 nm. For each formulation, three tablets were tested. The constants (k) of the release rate were calculated by the linear regression method:

$$\ln(M(\%) - M(\%)_t) = kt \qquad (7)$$

where $M(\%)$ is the percentage of the drug completely released (100%) and $M(\%)_t$ represents the percentage of the drug released at time t.

The mean dissolution time (MDT) was calculated using the Eqn 8:

$$\mathrm{MDT} = \frac{\int_0^\infty t \cdot (\mathrm{d}M(\%)/\mathrm{d}t) \cdot \mathrm{d}t}{\int_0^\infty (\mathrm{d}M(\%)/\mathrm{d}t) \cdot \mathrm{d}t} \qquad (8)$$

Simulation

Simulation was carried out on an IBM compatible personal computer with the implemented digital simulation language SIMCOS (Karba et al., 1990) and equipped with appropriate pharmacokinetic programs (Kozjek et al., 1983; Mrhar et al., 1990). Computer simulation enables the interpretation of pharmacokinetic profiles of drugs in a particular body compartment and gives, according to the mathematical model which consists of a system of first-order differential equations, an adequate solution to the problem. The identification procedure with an adaptive model was used for verification of the pharmacokinetic model structure. Integral square error was used as a criterion function.

Results and Discussion

The area between 70 and 90% of MC, 10 and 20% of HPMC and 10 and 20% of HPC (Fig. 1) in a three-phase diagram was chosen. 11 points for granulations with different compositions were determined (Table 1) and granulations with 10% of theophylline were prepared. The tablets produced from these granules had uniform shapes with flat surfaces and sharp edges. The values for k and MDT, calculated from the dissolution profiles, are listed in Table 2. Regarding the values for the parameter MDT it can be seen that the slowest release rate was exhibited by formulations 4 and 5 and, to a lesser extent, by formulations 1 and 3. Furthermore, the parameters k and MDT are not always in accordance, since single first-order release kinetics does not describe the dissolution pattern properly. It was therefore suggested that the dissolution profile is described by subsequent multiple first-order release kinetics. The parameter MDT, which is independent of the release kinetics, appears to be much more

TABLE 2

The values for MDT and k

Formulation	MDT (min)	k (min^{-1})
1	28.2	0.053
2	16.3	0.591
3	26.7	0.558
4	54.2	0.019
5	43.0	0.024
6	8.4	0.014
7	17.1	0.078
8	10.5	0.137
9	19.7	0.049
10	18.5	0.063
11	18.2	0.048

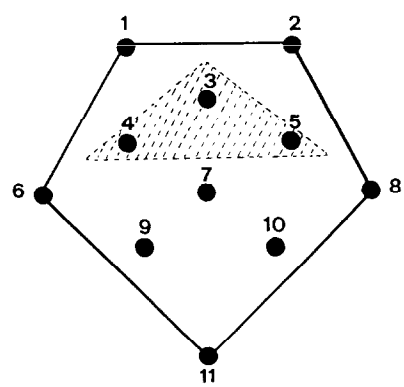

Fig. 2. New experimental domain selected.

TABLE 3

Results of multiple regression analyses

Formulation	Formulation factor			MDT (%)		Regression coefficient value of Eqn 2	
	B_1 (%)	B_2 (%)	B_3 (%)	Experimental [a]	Predicted [b]		
3	100	0	0	22.40	19.09	$b_1 (X_1)$	19.09
4	0	100	0	54.20	54.23	$b_2 (X_2)$	54.23
5	0	0	100	43.00	41.52	$b_3 (X_3)$	41.52
G	50	50	0	51.50	48.22	$b_{12} (X_1X_2)$	46.23
C	50	0	50	127.50	122.70	$b_{13} (X_1X_3)$	369.60
A	0	50	50	77.08	75.62	$b_{23} (X_2X_3)$	111.01
B	33.33	33.33	33.33	144.60	130.29	$b_{123} (X_1X_2X_3)$	903.93
E	66.67	16.67	16.67	80.00	94.71		
F	16.67	66.67	16.67	86.05	90.73		
D	16.67	16.67	66.67	102.10	111.32		

[a] Average of three determinations.

[b] Using Eqn 2.

appropriate for the evaluation of the dissolution results.

From the analysis of these results we selected a new experimental domain (Fig. 2).

We designed 10 experiments in this area using a simplex-centroid design (Mathieu and Phan-Than-Luu, 1992) where formulations 3–5 corresponded to the extreme vertices of simplex-

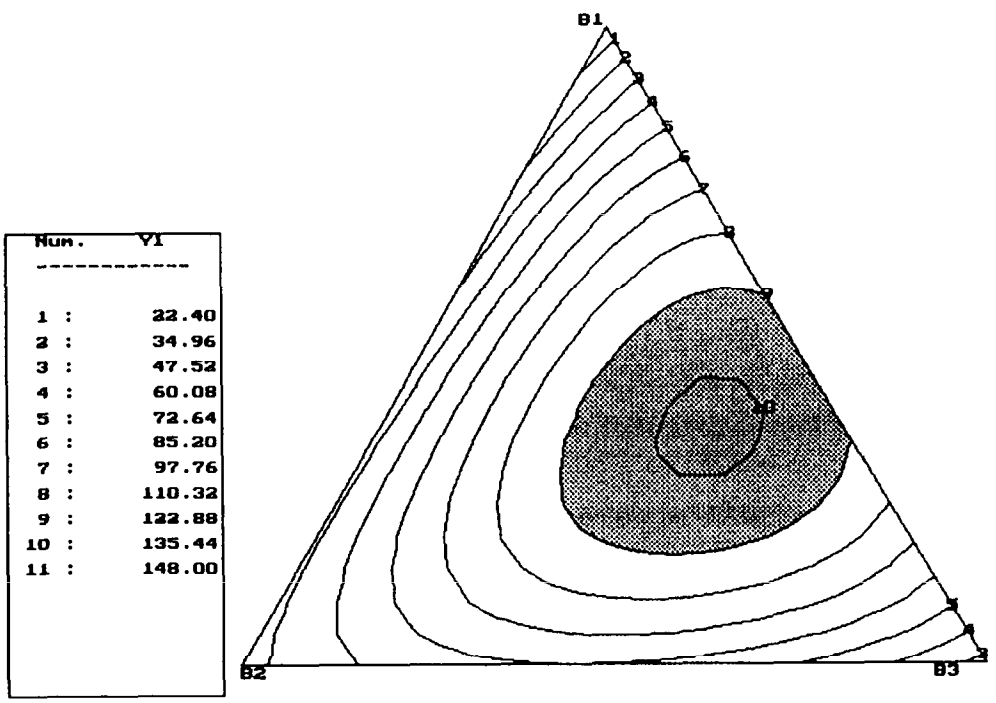

Fig. 3. The contour diagrams of MDT as a function of B_1–B_3.

centroid design, indicated by B_1–B_3, respectively.

The following mathematical model was postulated:

$$Y = b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{23}X_2X_3 + b_{13}X_1X_3 + b_{123}X_1X_2X_3 \quad (9)$$

The response Y_1 (mean dissolution time) was analyzed by regression analysis according to the proposed model (Eqn 9). The results are given in Table 3.

Fig. 3 shows the contour diagram of MDT as a function of B_1–B_3.

The granules designed, containing 10% of theophylline, were prepared and the tablets produced. The experimentally determined and predicted values for MDT, given in Table 3, are in good agreement. It is also evident that the release of theophylline from all formulations listed in Table 3 is more retarded than from those given in Table 1. The best retardation was exhibited by formulations B–D.

Finally, an attempt was carried out to produce tablets with 60 % of theophylline (300 mg), the therapeutic dose, which provides theophylline plasma oscillations between 10 and 20 mg/l when given at 8-h dosing intervals (Hendeles et al., 1984). For this purpose, granulation C containing 86.5% of MC, 11.75% of HPMC and 1.75% of HPC was used. For comparison, the theophylline formulation Euphyllina ritardo (BYK Gulden, Italy) was also tested, since it contains hydroxypropylmethyl cellulose (HPMC) as a retardation excipient. The values for MDT obtained from the dissolution profiles are very high for both formulations (185.0 and 201.0 min for formulation C with 60% of theophylline and Euphyllina ritardo, respectively).

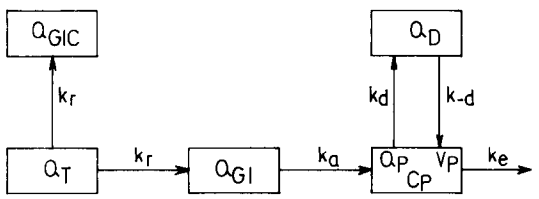

Fig. 4. Model for pharmacokinetic assessment of theophylline. Q_T, amount of theophylline in the formulation; Q_{GIC}, cumulative amount in the gastrointestinal tract; Q_{GI}, actual amount in the gastrointestinal tract; Q_P (C_P), amount (concentration) in the plasma (central compartment); V_p, volume of plasma (central compartment); Q_D, amount in the tissues (peripheral compartment). k, first-order rate constant; subscripts: r, in vitro release; a, absorption; d, −d, distribution; e, overall elimination.

TABLE 4

First-order release rate constants of theophylline from curve-fitting procedure of formulation C with 60% of theophylline and Euphyllina ritardo

Formulation	Formulation C with 60% of theophylline	Euphyllina ritardo
k_{r_1} (h^{-1})	0.79	0.54
Period (h)	0–0.1	0–0.05
k_{r_2} (h^{-1})	0.22	0.17
Period (h)	0.1–1.0	0.05–3.1
k_{r_3} (h^{-1})	0.18	0.33
Period (h)	1–3.6	3.1–4.3
k_{r_4} (h^{-1})	0.41	0.65
Period (h)	3.6–5.1	4.3–6.4
k_{r_5} (h^{-1})	1.0	1.36
Period (h)	5.1–8	6.4–8

The behaviour of both preparations in vivo was predicted by mathematical modeling and computer simulation. For this purpose, a two-compartment pharmacokinetic model was used (Fig.

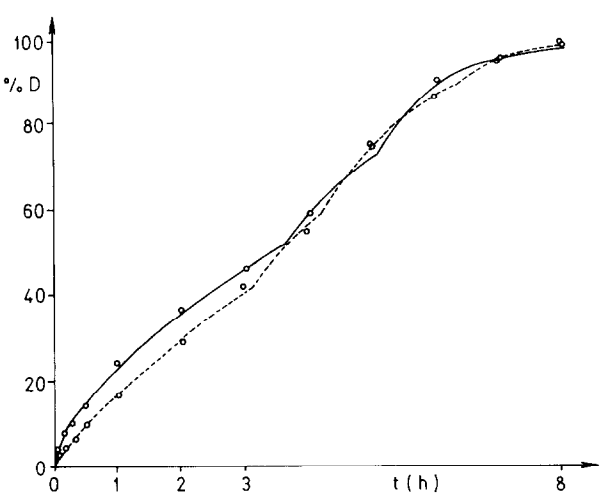

Fig. 5. Simulated theophylline dissolution profile from formulation C with 60% of theophylline (continuous line) and for Euphyllina ritardo (broken line). %D, percentage of the dose; (○) experimental data.

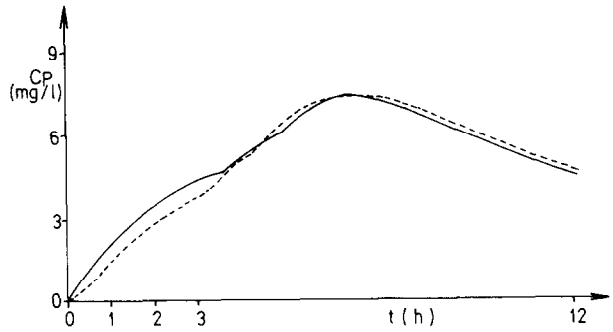

Fig. 6. Predicted plasma levels of theophylline after administration of a single dose of: (continuous line) formulation C with 60% of theophylline; (broken line) Euphyllina ritardo. $k_a = 2.29\ h^{-1}$, $k_d = 0.41\ h^{-1}$, $k_{-d} = 1.34\ h^{-1}$, $k_e = 0.15\ h^{-1}$ and $V_p = 20$ l.

4). Two different gastrointestinal compartments have been included in the model: a cumulative one which gives information similar to the in vitro dissolution profile of the drug and an actual one which simulates the levels comparable to those present in vivo (Fig. 4).

First-order release rate constants (k_r) were identified through a curve-fitting procedure (Karba et al., 1990) and are given for both formulations in Table 4 and Fig. 5. It was necessary to introduce a time dependency of the constant (k_r) and five different first-order release rate constants in order to enable appropriate curve fitting.

Plasma levels of theophylline after administration of a single dose of both formulations were obtained by using the average values of the theophylline parameters in the case when the two-compartment model is assumed: $k_a = 2.29\ h^{-1}$, $k_d = 0.41\ h^{-1}$, $k_{-d} = 1.34\ h^{-1}$ and $k_e = 0.15\ h^{-1}$, $V_p = 20$ l (Kozjek et al., 1983; Mrhar et al., 1990).

The results of simulation (Fig. 6) indicate that C_{max} is observed in about 7 h (T_{max}) after single administration for both formulations.

Finally, the model was used to explore the efficiency of a multiple-dose regimen taking into account 8- and 12-h intervals (Fig. 7). Both formulations provide theopohylline steady-state plasma concentrations remaining at the same level and oscillating within the same range of magnitude. It is evident that a theophylline dose of 300 mg is sufficient to maintain concentrations higher than the minimal effective concentration (10 mg/l) when given at 8-h intervals. It is suggested on the basis of the results obtained by simulation to increase the dose up to 450 mg if 12-h intervals are preferred.

Conclusion

The different compositions of cellulose derivatives, used in this study, have a considerable effect on the dissolution behaviour of the theo-

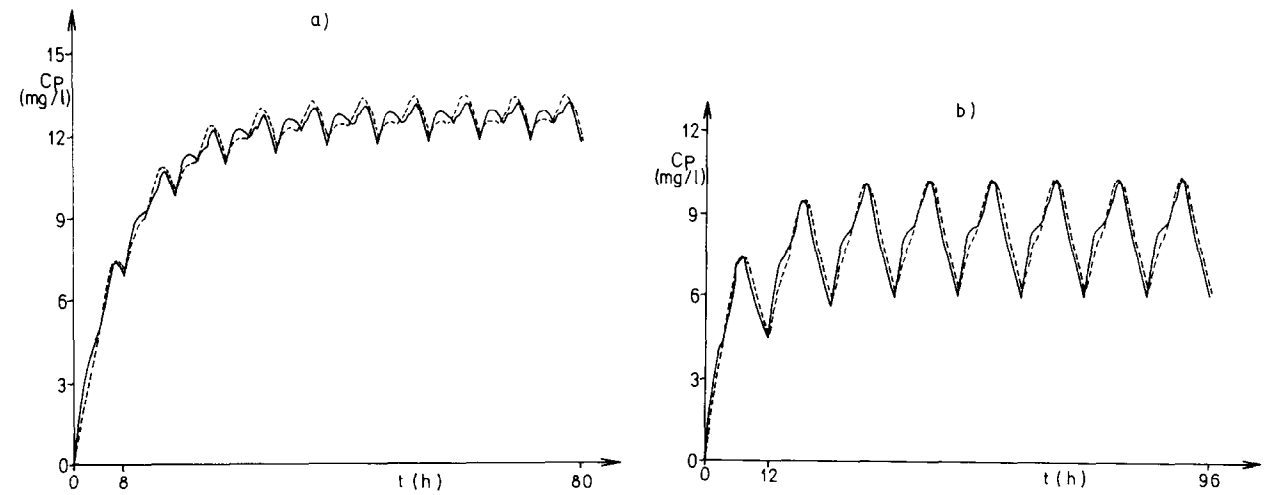

Fig. 7. Predicted plasma levels after administration of a multiple dose. (Continuous line) Formulation C with 60% of theophylline; (broken line) Euphyllina ritardo. (a) 8-h intervals; (b) 12-h intervals.

phylline present in tablets. The mixture approach used for experimental design represents an excellent tool for predicting the formulations with the best retardation properties. Regarding the simulation results, formulation C with 60% of theophylline and 40% of the excipients (86.5% of MC, 11.75% of HPMC and 1.75% of HPC) provides plasma concentrations of the drug within the therapeutic range after 8- and 12-h multiple-dosage regimens to the same extent as commercialy available tablets.

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