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Pharmacokinetic evaluation of sustained release formulations of theophylline by analog hybrid simulation

Aleš Mrhar [1], Fulvio Rubessa [2], Rihard Karba [1], Mariarosa Moneghini [2] and Stanislav Primosic [1]

[1] *University E. Kardely in Ljubljana, Faculty of Technology and Natural Sciences, Department of Pharmacy and Faculty of Electrical and Computer Engineering, Ljubljana (Yugoslavia) and* [2] *University of Trieste, Institute of Pharmaceutical Technology, Trieste (Italy)*

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Summary

Several new formulations of theophylline, loaded on polystyrene beads, were developed. Their sustained release performance was evaluated by in vitro dissolution test. Analog-hybrid simulation was carried out in order to evaluate the influence of some technological parameters on the pharmacokinetics of theophylline. Single- and multiple-phase processes of dissolution were proposed. Furthermore, predicted plasma levels in single- and multiple-dosage-regimen schemes were obtained. Formulations with a first-order release rate constant lower than 1.0 h^{-1} can be administered as a sustained release dosage form at 12-h intervals.

Introduction

The search for improved therapy and patient compliance has stimulated the development of new formulations of well-known drugs.

Oral theophylline therapy has been shown to be very effective in the treatment of acute and chronic aspects of asthmatic conditions. In order to achieve maximum therapeutic benefit with a low risk of severe side effects, the serum concentration should be maintained within the narrow range of 10–20 mg/l (Dahlquist et al., 1984). Because of the short half-life of theophylline a maintenance scheme of 6–8 h is required to avoid large fluctuations in plasma concentration. Within such a dose regimen, lack of patient compliance and inter- and intra-subject variability necessitated the design of sustained release dosage forms of theophylline (Hendeles et al., 1984).

The present study was undertaken in order to evaluate the influence of technological parameters of preparation of several dosage forms of theophylline, loaded on polystyrene beads (Lovrecich and Rubessa, 1987), on the pharmacokinetics of the drug. Analog-hybrid simulation was carried out to predict actual plasma concentration in single- and multiple-dosage-regimen schemes.

Correspondence: F. Rubessa, Institute of Pharmaceutical Technology, University of Trieste, Via Cumano 2, 34139 Trieste, Italy.

Materials and Methods

Materials

Theophylline (Farmitalia Carlo Erba) and polystyrene, cross-linked with 1% divinylbenzene (Biobeads SX-1, Biorad), were used as received. Solvents and buffers were of analytical grade.

Formulations

Procedure A: 8 ml of a chloroform solution of theophylline (6 mg/ml) were poured slowly onto 1 g of powdered polymer with continuous mixing in a mortar. After swelling the loaded polymer was dried to constant weight in an oven at 60 °C for 2 h, subsequently deaggregated with an 80 μm sieve and mixed.

Procedure B: 1 g of the polymer was suspended in 25 ml of a chloroform solution of theophylline (6 mg/ml). The resultant system was stirred at room temperature for a predetermined period of time and filtered. The loaded polymer was dried in an oven at a predetermined temperature to constant weight. Finally, it was deaggregated with an 80 μm sieve and blended.

Preparation data for the formulations are listed in Table 1.

Methods

Dissolution rates

Phosphate buffer (900 ml; pH 7.5) was placed in a rotating paddle apparatus (USP XXI) at 150 rpm and maintained at 37 ± 0.2 °C. A weighed sample of loaded polystyrene was placed in a capsule and introduced at the bottom of the vessel. At predetermined time intervals up to 3 h, 5.0-ml sample volumes were removed from the solution, filtered through a 0.45 μm pore size filter (Millipore, France) and assayed spectrophotometrically (Perkin Elmer, model 552 spectrophotometer) at 271 nm. An equal volume of fresh buffer was then added to the dissolution medium. Sink conditions were maintained. Each experiment was performed in triplicate and the mean experimental values were within 5%.

TABLE 1

Preparative conditions and composition of the formulations

Formulation no.	Procedure of preparation	Time of suspension (days)	Temperature (°C)	Drug content (mg/g)
1	A	–	60	40
2	B	1	60	28
3	B	3	60	32
4	B	7	60	37
5	B	7	4	37
6	B	7	40	37
7	B	7	80	37

Analog-hybrid simulation

Simulations were carried out with an analog-hybrid computer (Electronics Associates, model EAI-580) equipped with the appropriate pharmacokinetic programs (Kozjek et al., 1983; Kmetec et al., 1984). Computer simulation enables the interpretation of the pharmacokinetic profiles of drugs in a particular body compartment. According to the mathematical model, which consists of a system of first-order differential equations, the analog-hybrid computer ensures an adequate solution of the problem and the possibility of modifying and completing the model during the process of simulation. The identification procedure with an adaptive model was used for verification of the pharmacokinetic model structure. Parameters were modulated manually on the computer in order to obtain optimal accordance between the model response and the experimental data. Integral square error was used as a criterion function (Mrhar et al., 1984).

Results and Discussion

Pharmacokinetic modelling

Pharmacokinetic compartmental analysis, based on the analog-hybrid simulation, was carried out with the use of the composed two-compartment model (Fig. 1). It consists of distinct compartments representing sustained release formulation, cumulative gastrointestinal, actual gastrointestinal, plasma (central) and tissue (peripheral) regions.

Two different gastrointestinal compartments have been included in the model: a cumulative

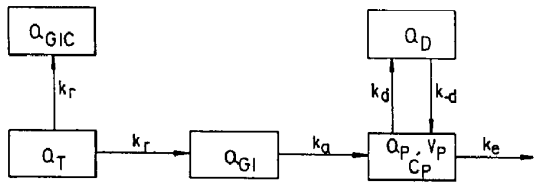

Fig. 1. Model for pharmacokinetic assessment of theophylline. Q_T, amount of theophylline in the formulation; Q_{GIC}, cumulative amount in the gastrointestinal tract; Q_{GI}, actual amount in the gastrointestinal tract; Q_P (C_P), amount (concentration) in the plasma (central compartment); Q_D, amount in the tissues (peripheral compartment). k, first-order rate constant; subscripts: r, in vitro release; a, absorption; d, −d, distribution; e, overall elimination.

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.

First-order rate release constants (k_r) were identified through a curve-fitting procedure (El-Yazigi and Sawchuk, 1985) on an analog-hybrid computer. Typical results are reported in Fig. 2.

As a first approach, only one k_r was established but the fitting was unsatisfactory. Only a physical mixture of the drug and the polymer gave excellent correlation. This can be explained by the fact that the drug is dissolved without any physical interaction with the polymer. Consequently, the model was modified by introducing a time dependency of the constant k_r. In formulation 1, two phases enabled us to achieve better fitting. Furthermore, a triple-phase dissolution profile was obtained for formulation 5 while formulations 2–4,

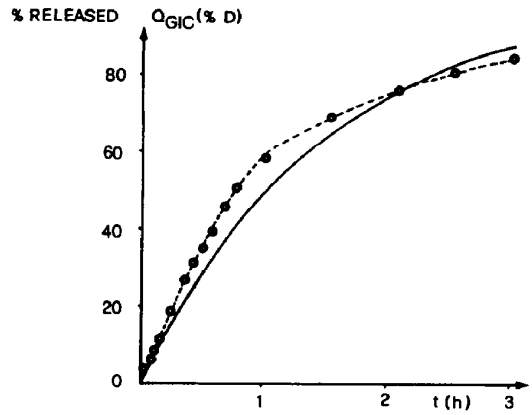

Fig. 2. Theophylline dissolution profiles for formulation 1. %D, percentage of the dose; (○) experimental data; (———) one-phase and (- - - -) multiple-phase simulated profiles.

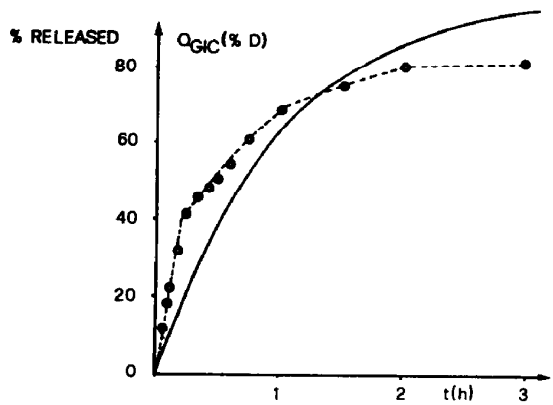

Fig. 3. Theophylline dissolution profiles for formulation 4. %D, percentage of the dose; (○) experimental data; (———) one-phase and (- - - -) multiple-phase simulated profiles.

TABLE 2

First-order release rate constants of theophylline from curve-fitting procedure

Formulation no.	k_r (h^{-1})	k_{r1} (h^{-1})	Period (h)	k_{r2} (h^{-1})	Period (h)	k_{r3} (h^{-1})	Period (h)	k_{r4} (h^{-1})	Period (h)
1	0.7	1.0	(0–1)	0.5	(1–3)				
2	4.0	9.9	(0–0.1)	3.3	(0.1–0.45)	1.1	(0.45–1.0)	0.6	(1.0–3.0)
3	1.5	3.7	(0–0.2)	1.7	(0.2–0.6)	0.6	(0.6–1.8)	0.07	(1.8–3)
4	1.0	2.7	(0–0.2)	0.8	(0.2–1)	0.4	(1–2)	0.04	(2–3)
5	1.8	3.9	(0–0.3)	1.0	(0.3–0.9)	0.07	(0.9–3)		
6	1.3	4.3	(0–0.15)	1.4	(0.15–0.4)	0.65	(0.4–1.6)	0.1	(1.6–3)
7	1.2	3.3	(0–0.2)	1.0	(0.2–0.5)	0.7	(0.5–1.2)	0.05	(1.2–3)
Physical mixture	1.8								

k_r, overall release rate constant; k_{ri} ($i = 1$–4), partial release rate constant.

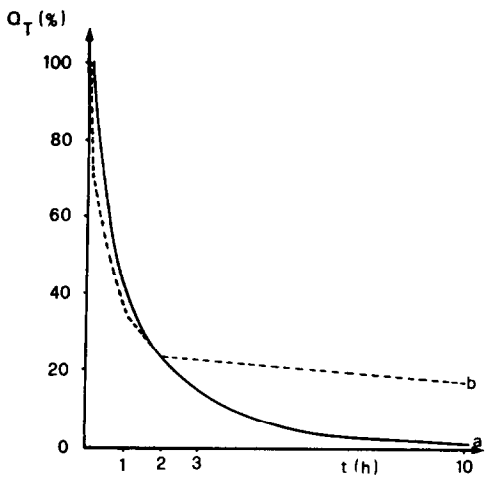

Fig. 4. Simulated profile of theophylline in dosage form. (a) Formulation 1, (b) formulation 4.

6 and 7 exhibited a quadruple-phase profile (Fig. 3).

Table 2 summarizes the values of identified in vitro release rate constants.

In Fig. 4 the predicted amounts of drug remaining in the dosage form during a period of 10 h are shown. It was assumed that absorption from the gastrointestinal tract to the central compartment occurs over the same period of time.

The model predicts that formulation 1 ensures complete dissolution within 10 h while experimental data indicate that only 85% of the drug is released within 3 h. In formulation 4, the percentages released after 3 and 10 h lie within the range of about 80% and the difference is very small. This observation is in agreement with the fact that the drug is incorporated into the core of the polymeric network during the process of loading and consequently a slow and incomplete release rate of the drug occurs.

Single-dose regimen

Plasma levels of theophylline after administration of a single dose of the seven formulations were determined by using the average values of the parameters for theophylline in the case of the two-compartment model being 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} (Kozjek et al., 1983).

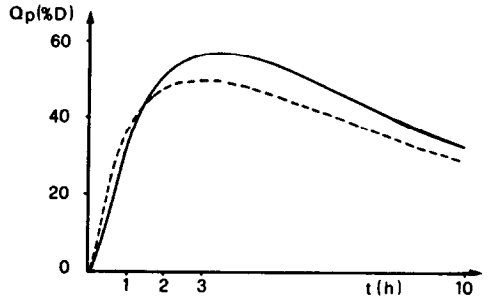

Fig. 5. Predicted plasma levels of theophylline after administration of a single dose of formulation 1. (———) Single phase, (- - - - -) multiple phase.

The results of simulation (Figs 5 and 6) indicate that C_{max} is reached in about 3 h (T_{max}) and is consistent irrespective of the approach for the interpretation of the dissolution profiles. Furthermore, this last statement is valid for the whole set of formulations under investigation.

Multiple-dose regimen

Finally, the model was used to explore the efficiency of a multiple-dose regimen taking into account 6-, 8- and 12-h intervals.

Simulated profiles are reported in Fig. 7 using the k_r values obtained for the single-phase process of dissolution.

Formulation 1, which exhibits the lowest k_r value, ensures oscillations of theophylline plasma levels within the therapeutic range. In contrast, formulation 2 which has the highest k_r value yields much higher oscillations in levels which exceed the minimal toxic dose and fall below the minimal effective concentration.

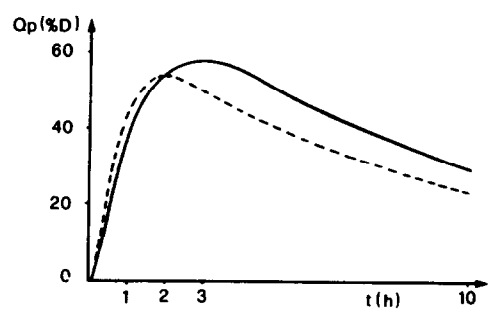

Fig. 6. Predicted plasma levels of theophylline after administration of a single dose of formulation 4. (———) Single phase, (- - - - -) multiple phase.

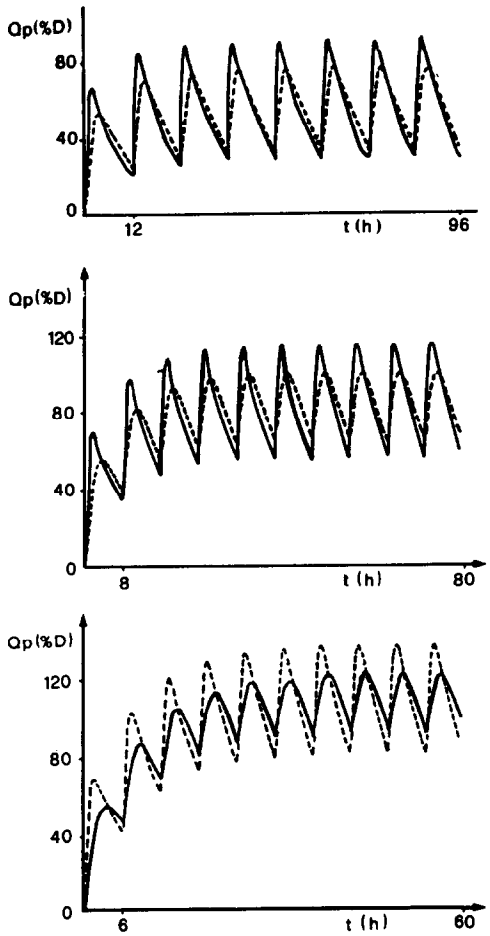

Fig. 7. Predicted plasma levels of theophylline after administration of a multiple dose. (———) Formulation 1, (- - - - -) formulation 2.

Overall, the results obtained allow us to conclude that a formulation with a k_r value lower than 1.0 h^{-1} can be claimed to be a sustained release dosage form provided it is administered in a 12 h multiple-dosage-regimen scheme.

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