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The megaloporous system: a novel principle for zero-order drug delivery I. In vitro and in vivo performance

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Summary

In vitro dissolution tests (USP XX paddle apparatus at 100 rpm and USP XX dissolution apparatus 3) were used to evaluate the drug release from a commercial preparation (Theolin retard) and from two megaloporous systems, performed in both acidic (pH 1) and buffered medium (pH 6.8). Theolin retard demonstrated a biphasic drug release pattern, which appeared to be sensitive to the pH and the dissolution model. In acidic conditions, the theophylline extraction rates from the megaloporous systems, the one prepared with Eudragit RS polymer (preparation B) and the other partly with Eudragit L polymer (preparation C), were constant, similar and independent of the dissolution model applied. In buffered medium, the rate of drug delivery from preparation B was found to be lower in the paddle apparatus and from preparation C faster in the dissolution apparatus 3, when compared to the rates in the respective models at pH 1. The dosage forms have been evaluated and compared with a neutral solution (preparation D) in a single dose study (latin-square design) in 8 healthy volunteers. Both, maximum concentration of the drug in plasma from Theolin retard ($C_{max} = 5.8 \pm 1.6$ μg/ml), preparation B ($C_{max} = 3.2 \pm 1.1$ μg/ml) and preparation C ($C_{max} = 4.4 \pm 1.9$ μg/ml) and peak times (9.0 ± 1.7, 8.4 ± 1.6 and 7.8 ± 1.7 h, respectively) were significantly different from the neutral solution (9.5 ± 1.8 μg/ml and 2.0 ± 0.5 h). No significant difference between complete absorption and the extent of drug released was found for either Theolin retard ($96 \pm 16\%$, $0.2 < P < 0.25$) or preparation C ($87 \pm 20\%$, $0.05 < P < 0.10$). Preparation B released its theophylline content incompletely during the 32 h of the plasma measurements, i.e. $75 \pm 24\%$ ($P < 0.025$). A value for the deviation of the ideal performance in vivo (DIP) is introduced to compare the in vivo release from oral controlled release dosage forms to the ideal performance in vivo, i.e. 8.33% of the drug content released each hour in the first 12-h period after administration. For Theolin retard and preparation C this value was found to be similar and considerably lower than the mean DIP value for preparation B. Comparison of the in vitro drug delivery from preparation C and Theolin retard with the release in vivo reveals, that the rate of theophylline release in the two dissolution models appears to be about 1.5 times higher than the rate for both preparations in vivo.

Introduction

This paper reports the in vivo release results of two preparations, delivering 70–80% of the theophylline content in vitro at a constant rate. The preparations will be referred to as megaloporous systems. A model for the mechanism of drug release from the megaloporous system will be published (De Haan and Lerk, 1985).

Theolin retard (Theodur in the U.S.A.) was included as reference, since this product has demonstrated adequate controlled release properties

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with complete bioavailability (Dasta et al., 1979; Weinberger et al., 1978), approaching the ideal of a constant drug delivery more closely than other available products (Hendeles et al., 1984).

This study focuses on both the rate and the extent of theophylline release from the three preparations, in vitro as well as in vivo.

Experimental

Preparations

Tablet A [1] was a solid dosage form, comprising of coated spherical pellets, which were embedded in a slow dissolving substance.

Tablet B and tablet C

The two types of granules, used to constitute the *housing matrix phase* and the *restraining matrix phase* of the megaloporous system (De Haan and Lerk, 1985), were prepared separately as follows.

TABLE 1

	Composition of the housing phase	
	HMG I	
Carboxyvinyl polymer [1]	7.5 g	
Polyethylene glycol 6000	36.2 g	
Lactose (Ph. Eur. pulv.)	36.6 g	
Magnesium stearate	1.8 g	
Emcompress [2]	21.8 g	
	Composition of the restraining phase	
	RMG I	RMG II
Eudragit polymer [3]	20.0 g (RSPM)	15.0 g (L)
Theophylline monohydrate (Ph. Eur.)	70.9 g	70.9 g
Cetyl alcohol	5.0 g	–
Talc	10.0 g	–
Emcompress [2]	–	20.0 g

[1] Carbopol 934, B.F. Goodrich, U.S.A.
[2] Mendell Co, New York, U.S.A.
[3] Röhm Pharma, Darmstadt, F.R.G.

[1] Theolin retard (300 mg), Astra Chemicals Benelux BV. Rijswijk (Netherlands). Lot number 82 L 27 H M-394.

Type A. Granules were made according to the formulation shown in Table 1. Polyethylene glycol 6000 particles were reduced to a particle size smaller than 180 μm in a laboratory mill-apparatus. Theophylline monohydrate and lactose were passed through a 180 μm screen. Carboxyvinylpolymer was added and the powders were dry-blended in a Turbula mixer to a homogeneous mixture. Magnesium stearate was bolted through a 220 μm screen and added to the blend. Mixing was proceeded for another two minutes. The resulting mass was heated in an oven at 90°C until sticky and then immediately extruded in an Alexander granulator. The solidified particles were passed through a comminuting machine (Frewitt granulator, screen openings 2 mm) and subsequently screened through openings of 1.0–1.6 mm. This fraction was collected for use and will be referred to as the *housing matrix granulation.* The formulation used in tablet B and tablet C is designated as HMG I.

Type B. A granulation, having the composition shown in Table 1 was prepared by mixing the drug, the polymer (Eudragit RSPM), talc and Emcompress (< 180 μm) in an evaporating dish and wetting the mixture with an excess of chloroform. Cetylalcohol, where included, was dissolved in the chloroform (acetone was used in the case of Eudragit L polymer). The mixture was continually stirred and evaporated off until a pasty granuable smooth slurry was obtained. The mass was granulated by means of a 1.6 mm screen and then allowed to dry. The spaghetti-like material was crushed by a Frewitt granulator (screen-openings 2 mm) and screened to the desired particle size (in this study 1.4–1.6 mm). The fraction, collected for use, was dried for 24 h at 40°C. This extruded, sized and dried material is called the *restraining matrix granulation.* The two formulations used, as shown in Table 1, are designated as RMG I and RMG II.

Tablet B and tablet C were cylindrical devices (diameter 13 mm), composed of 472 mg of RMG I (see Table 1) and 236 mg of RMG I + 236 mg of RMG II particles (1.4–1.6 mm) respectively and 543 mg of HMG I particles (1.0–1.6 mm), corresponding with 300 mg of anhydrous theophylline for each tablet formulation. The applied compac-

tion pressure was 73×10^3 kN · m^{-2}.

A neutral solution (preparation D), containing 300 mg anhydrous theophylline in 200 ml of water, was used as a reference.

Subjects

Eight healthy volunteers (4 males and 4 females), age 21–27 years (mean 24), weighing 54–71 kg (mean 63), heights 1.70–1.86 m (mean 1.77), participated in the study after a written informed consent was obtained. Three were habitual smokers (subject 3, 5 and 7; 10–20 cigarettes/day), subject 1 only smoked on special occasions and four were non-smokers.

In vitro drug release

The in vitro drug release studies were performed by means of both the dissolution apparatus 1 (paddle) and 3 (modified disintegration tester), as described in the USP XX/NF XV. Each preparation was tested 4 times in deaerated dissolution medium (0.1 N hydrochloric acid or phosphate buffer (Ph. Eur) pH 6.8). Aliquots of the dissolution medium were assayed for theophylline by ultraviolet spectrophotometry. The release rate of theophylline is *only* expressed in mg/h, when the rate is substantially constant in the particular time period.

Study design

The theophylline preparations were given to the volunteers in a latin-square design. The solid dosage forms were administered with 200 ml of water. The neutral solution of theophylline (200 ml) was taken over a period of 1 h (10 ml portions at 3-min intervals, with the first 10 ml ingested at t = 1 min 30 s). The complete study was carried out within a 5-week period, with a wash-out period of about one week after each administration.

The subjects were asked to refrain from alcoholic beverages and caffeine or theobromine containing beverages or food for 24 h before and on the day of blood sampling and to take no drugs for 7 days before and during the entire study.

All volunteers were fasted, with the exception of water, for 12 h prior to dosing. A light meal was served 4 h after dosing. A light dinner was taken at about 9–11 h after drug administration. Predose blood samples (10 ml) were obtained immediately before dosing via an indwelling catheter or by venapuncture (Venojects) in a forearm vein. After dosing, blood samples were collected at 1, 2, 3, 4, 5, 6, 7, 8, 9, 24, 26, 28 and 32 h. Just prior to the dosing and at 4, 5, 6, 7, 8, 9, 10, 12, 14, 16 and 24 h, the volunteers expectorated about 2 ml of mixed saliva. The volunteers chewed, when necessary, some Parafilm to stimulate the saliva flow.

Saliva and plasma (separated from the whole blood by centrifugation) samples were stored at −18°C until analysis.

Assay procedure

Plasma and saliva theophylline determinations were made by high-pressure liquid chromatography (HPLC) according to a method, proposed by Jonkman (1984). To 1.0 ml of serum or saliva was added 100 µl of an internal standard solution of β-hydroxyethyltheophylline in water (1 : 5000) and 1000 µl of a saturated ammoniumsulphate solution. After mixing on a Vortex mixer for 10 s at maximum velocity, 2.0 ml of extraction solvent (chloroform–isopropanol (20 : 1)) was added and mixing was continued for 60 s. The mixture in the tubes was centrifugated for 5 min and the supernatant aqueous layer, frozen in liquid nitrogen, was separated from the organic phase. About 50 µl of the remaining organic phase was injected on the straight phase column [2] (25 cm, 4.6 mm i.d.). The chromatograph [3] was fitted with a UV (280 nm) absorbance detector [4] (sensitivity scale 0.02 a.u.f.s.) and a computing integrator [5] for computing the peak heights. The mobile phase was prepared by mixing 30 ml of methanol, 550 ml of *n*-heptane and 420 ml of chloroform and prior to use degassed and filtered. All determinations were performed at least in duplicate at ambient temperature with a solvent flow rate of 2.6 ml/min.

Pooled plasma samples, spiked with known concentrations of theophylline were prepared and analyzed daily to allow calculation of a standard theophylline concentration curve by comparing

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[2] Lichrospher 100-Si-10.
[3] SERIES 10 Liquid Chromatograph, Perkin Elmer.
[4] Absorbance Detector Model 441, Waters.
[5] Minigrator, Spectra Physics.

the peak height ratio of theophylline to β-hydroxyethyltheophylline to the spiked plasma theophylline concentrations.

The assay demonstrated a sensitivity of 0.4 μg/ml and linearity to at least 15 μg/ml. The ability to distinguish theophylline from its metabolites was satisfactory. The average correlation coefficient of the standard curves was 0.9997 and the coefficient of variation of the slopes of the regression lines 1.3%.

Data treatment

For each subject after a particular dose, the S/P ratio was calculated for the plasma and saliva concentrations, sampled simultaneously (4, 5, 6, 7, 8, 9 and 24 h in the sampling schedule). With the ratio, plasma concentrations of theophylline at 10, 12, 14 and 16 h were calculated from the saliva samples at these times. The mean (± S.D.) of the S/P ratio in all volunteers was found to be 0.68 ± 0.12. In this study, the mean coefficient of variation between the sampling times in the 8 × 4 series was 10 ± 7%.

The paired Student's *t*-test was performed to detect differences between the plasma peak-levels and peak-times.

The rate and extent of in vivo availability for absorption of theophylline from the three controlled release dosage forms was assessed by a numerical deconvolution method (Proost and Lerk, 1985a). Deconvolution can only be properly applied if the response to a unit dose impulse input is linear. In other words, the plasma profile following the administration of the oral solution should obey linear pharmacokinetics. It is assumed that the theophylline after being released from the controlled release dosage forms exhibits the same pharmacokinetic profile as the orally administered solution of the drug, independent of the moment of drug release.

The neutral solution of theophylline was administered within the first hour at a pseudo-constant rate. This procedure allows an accurate estimation of the partial integrals of the unit dose response function (Proost and Lerk, 1985a). In order to increase the stability with regard to data noise, the double-interval damping procedure was applied. The weighting factors were chosen $Q_1 = 0.125$ and $Q = 0.25$, which were shown to give rather smooth input profiles without serious deformation (Proost and Lerk, 1985b and c).

Difference of completeness of theophylline delivered in vivo was analyzed with the Student's *t*-test, comparing the total percentage released by the controlled release preparation with 100%. By application of the paired *t*-test to the percentages released at sequential sampling times, the moment was detected, after which no significant drug delivery could be determined.

The confidence limits of the in vivo theophylline release, enclosing the shaded area in the Figs. 1A, B and C, were obtained by plotting the mean plus and minus the standard deviation of the percentage released at each sampling point.

The *deviation of ideal performance* (DIP) is introduced as a simple and objective value in the assessment of the in vivo performance of a controlled release system in a single dose study. The *ideal performance* (IP) may be defined as a zero-order release during a time T at a rate 1/T. The DIP value of an in vivo release profile is calculated with the equation:

$$DIP = \frac{\sum_{i=1}^{n} \left| P_{t_i} - \frac{t_i}{T} \right|}{\sum_{i=1}^{n} \frac{t_i}{T}}$$

in which P_{t_i} = the fraction of the drug content of the dosage form released at time t_i (h); t_i/T is the ideal fraction released in vivo at t_i, n = the number of equally spaced time points, where $t_n = T$. The denominator in the equation equals the maximum deviation in the time period studied, i.e. no drug release at all in vivo from the dosage form. The DIP value should be calculated for each individual release profile.

In this study, T was taken at 12 h; the sampling times of the data applied in the calculation were taken at 1-h intervals up to 12 h after administration. For that reason interpolation of the fractions released at 10 and 12 h was necessary to determine the fraction of theophylline delivered by the devices at 11 hours after ingestion.

Results and Discussion

Delivery of theophylline in vitro

To detect the effect of hydrodynamics and mechanical stress on the release of theophylline from the three controlled release dosage forms, the in vitro dissolution studies were performed in both the paddle model and the modified disintegration model (De Haan and Lerk, 1982), according to apparatus 1 and 3 from the USP XX/NF XV. Moreover, the effect of the pH was tested by comparing the results of trials in acidic (pH 1) and buffered medium (pH 6.8), respectively.

The results of the mean cumulative percentage of theophylline released versus time are plotted in the Figs. 1A, B and C.

In acidic medium, the release profiles of Theolin retard showed a considerable difference in the release rate in the first 5-h period within both dissolution models (59.6 ± 8.6 and $67.7 \pm 10.2\%$ in apparatus 1 and 3, respectively). After a total exposure of 8 h 80.1 ± 3.2 and $91.3 \pm 5.5\%$ was delivered in the paddle and disintegration model, respectively.

At pH 6.8, the rate of drug release from the commercial product was found to be increased. In the disintegration tester, a fast and almost constant release was exhibited, which was virtually completed after 6 h. The paddle apparatus showed a total release of $92.8 \pm 3.9\%$ in 8 h. Both results indicate a pH dependency of the theophylline release from Theolin retard (Theodur). This finding is consistent with the in vitro data presented by Simons et al. (1982), obtained by a release study on 100 mg Theodur tablets in the USP XIX rotating basket (100 rpm) with trials in simulated gastric (pH 1.2) and intestinal fluid (pH 7.4). It is interesting to note that the release plots of Theolin retard show, with the exception of the results at pH 6.8 in the modified disintegration tester, a characteristic biphasic profile. The first wave reflects the drug, principally released by the slow dissolving uncoated portion of the device, which contains about 35% of the theophylline content. The second part of the release profile is mostly determined by the drug, delivered by the coated spherical particles, which are released to the extraction liquids by the slowly dissolving parts of

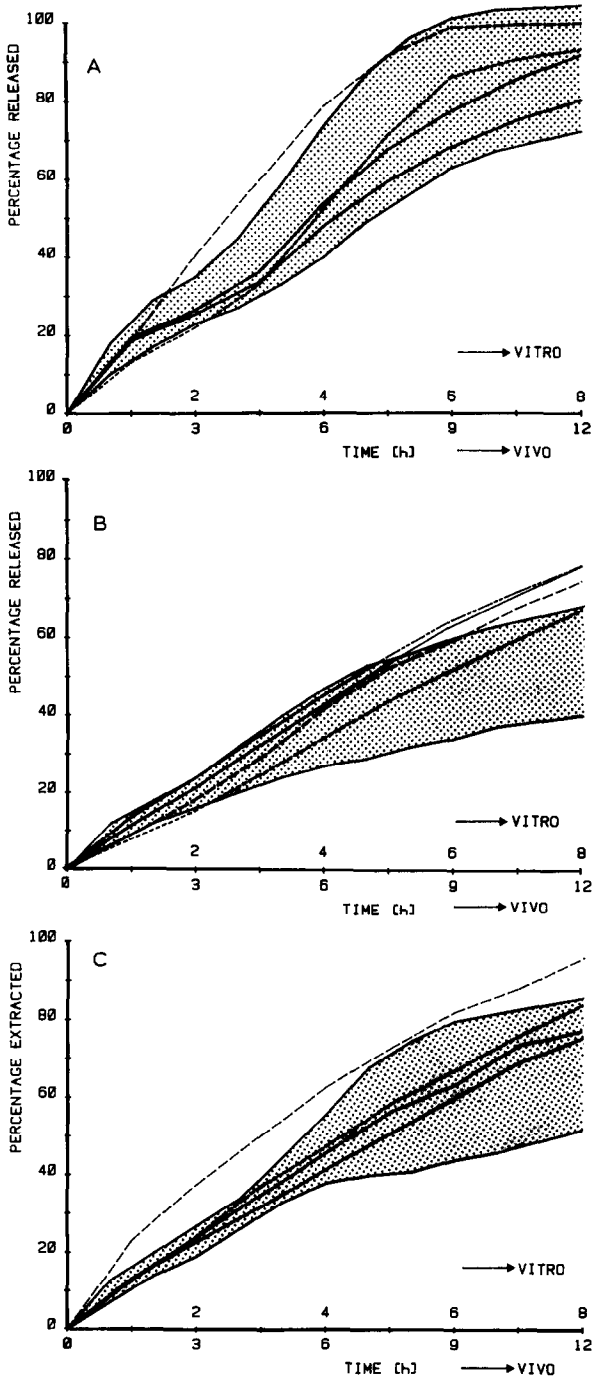

Fig. 1. A: percentage of theophylline released in vivo and in vitro from preparation A. Shaded area represents the confidence interval of the theophylline release in vivo. Release curves in vitro. Paddle apparatus 100 rpm: pH 1 ———; pH 6.8 - - - - - -. Apparatus 3 USP XX: pH 1 —·—·—; pH 6.8 — — —. B: percentage of theophylline released in vitro and in vivo from preparation B. C: percentage of theophylline released in vitro and in vivo from preparation C.

the device. This part appears to be affected markedly by the agitation and the pH of the liquids. This is most obviously revealed in dissolution apparatus 3 (Fig. 1A). The effect of the pH is caused by the cellulose acetate phthalate in the coating, which dissolves at pH 6.8.

Both megaloporous systems (Fig. 1B and C) show in acidic medium constant and similar rates of theophylline extraction in an 8-h period (29.3 ± 1.4 and 28.4 ± 0.7 mg/h in the paddle apparatus and 29.4 ± 1.0 and 29.1 ± 1.0 mg/h in the modified disintegration tester for preparation B and C, respectively). The data show that the drug extraction rates from both megaloporous preparations are substantially independent of the agitation conditions and mechanical stresses, exerted by the two dissolution models. In the paddle design, only a few restraining particles were dislodged from the devices during the extraction process, whereas a complete disintegration had occurred after 6–7 h in the modified disintegration tester. Exposure of the tablets to the buffered dissolution medium with a pH of 6.8 showed, however, a clear distinction in release behaviour between preparation B and C.

The rate of drug delivery from tablet B was, compared to acidic medium, impaired in both the paddle model (25.1 mg/h) and the disintegration apparatus (27.8 ± 1.3 mg/h). The shift may be explained by the gel-structure formed by the carboxyvinyl polymer in the megalopores at this pH, exerting a barrier for water penetration and drug transport. Drug extraction from preparation C was found to be slightly affected by the pH of the medium in the paddle apparatus (31.6 ± 3.8 mg/h), but was strongly increased in the disintegration model, resulting in a profile, which deviated from linearity (Fig. 1C). The slow dissolution of Eudragit L in the composition of RMG II in the buffered medium (pH 6.8) offsets the impairing effects of the carboxyvinyl polymer on the drug extraction process in the paddle model (Fig. 1C). In the disintegration model, particles are relatively fast dislodged, since the restraining phase structure in the system is subverted by the slowly dissolving granules of the RMG II formulation. This results in a rapid theophylline release with a consistently declining rate.

The megaloporous preparations showed little variability in the release rates, irrespective of the dissolution model, in particular at pH 1. The commercial product demonstrated higher variability in the release of theophylline, e.g. after 4 h of immersion, standard deviations of 9.8 and 20.5% in the paddle apparatus and 12.1 and 7.6% in the disintegration tester were found at pH 1 and 6.8, respectively.

Delivery of theophylline in vivo

All subjects, except subject 8, showed the same rank order in the theophylline level in the absorption phase, i.e. decreasing levels in the rank order of preparation D, A, C and B. Because mean concentration–time profiles are easily misinterpreted, the data of only one subject, which may be considered representative, are illustrated in Fig. 2. The differences in the slope of the decreasing part of the plasma levels, when compared with the elimination part of the profile from the solution, indicate a continued absorption from the solid dosage forms, in particular from preparation B (Fig. 2).

Table 2 gives information on the mean peak time (t_{max}) and the mean plasma peak concentration (C_{max}). Administration of the solution showed significantly shorter peak times (2.0 ± 0.5 h) as compared to preparation A (9.0 ± 1.7 h), preparation B (8.4 ± 1.6 h) or preparation C (7.8 ± 1.7 h). The peak levels generated (5.8 ± 1.6 μg/ml, 3.2 ± 1.1 μg/ml and 4.4 ± 1.9 μg/ml, respectively for preparations A, B and C) differed significantly from the neutral solution ($P < 0.05$).

The in vivo release data demonstrate significant drug delivery from preparation B and C up to 32 h after administration ($P < 0.05$), whereas significant release from preparation A could be found up to 16 h only ($P < 0.05$). Statistical analysis showed no significant differences from complete delivery of theophylline from preparation A and preparation C at 24 and 32 h, respectively (Table 3). A slow and incomplete release was found for preparation B in the entire period (32 h) of plasma theophylline measurements ($P < 0.025$).

Fig. 3A, B and C reflect the deviation of the calculated in vivo release from the ideal of zero-order release (DIP). The straight line represents a

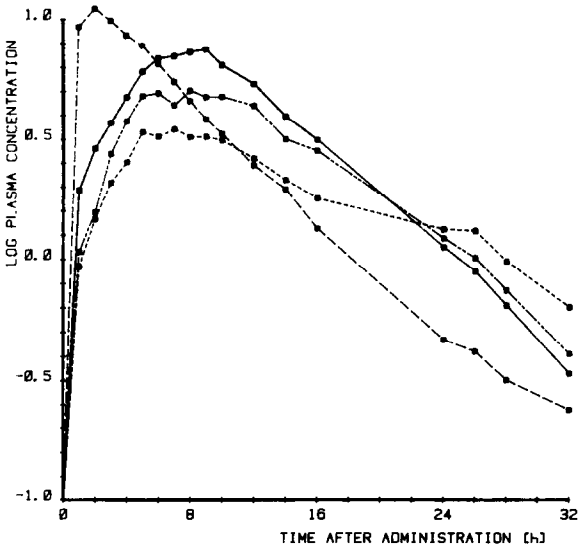

Fig. 2. Plasma concentration–time profiles after administration of: preparation A ———; preparation B - - - - -; preparation C — - - —; and preparation D — — —.

constant drug delivery of 100% in 12 h, i.e. 8.33% per hour, enabling convenient dosing twice a day.

The data from preparation A are plotted in Fig. 3A. The points of inflection are remarkable, present at about 4 h after administration. The results show very sharp increasing and decreasing in vivo release rates, providing a large inter-individual variation.

For preparation B, decreasing drug delivery rates were found over a period of 12 h for most of the subjects (Fig. 3B). The extent of theophylline availability from the device was $54 \pm 14\%$ in 12 h, whereas only $75 \pm 24\%$ of the content was delivered after 32 h. Fig. 3C shows the in vivo drug release curves from preparation C in relation to the ideal performance. It should be noted, that the preparation initially exhibited almost constant in vivo release, with remarkably low inter-individual variation. By testing the coefficients of variation of the percentages released at each time point from the 8 series, a significantly lower inter-individual variability could be found for preparation C up to 8 h after administration, when compared with preparation B ($P < 0.02$) and with preparation A ($P < 0.05$). At longer times, drug delivery tails off considerably, resulting in an amount released of $69 \pm 17\%$ at 12 h after ingestion of the device. In two subjects the drug delivery rate was found to increase after 4 h.

TABLE 2

	Peak time (h)	Peak level (μg/ml)
Preparation A	9.0±1.7	5.8±1.7
Preparation B	8.4±1.6	3.2±1.1
Preparation C	7.8±1.7	4.4±1.9
Preparation D	2.0±0.5	9.5±1.8

Application of the method introduced for the assessment of the in vivo performance of controlled release dosage forms resulted in the largest mean DIP-value for preparation B (0.36 ± 0.15; Table 4). This is not surprising, when the continuous decay in the release rate from preparation B is considered over the 12-h period (Fig. 3B). Preparations C and A demonstrated similar DIP-values (0.22 ± 0.12 and 0.23 ± 0.12, respectively). For preparation C the height of the DIP-value is mainly determined by the performance in the 8–12-h period after ingestion of the device, in which the drug extraction rate decreased, whereas for Theolin retard most contribution is provided in the period of 5–9 h after administration, in which theophylline delivery was rather fast (Fig. 3A and C).

In vitro / in vivo correlation

In vitro drug release studies in dissolution models with trials performed at pH 1 alongside pH 6.8 may provide unambiguous information on potential pH sensitivity of the drug release rate from a particular device. As a matter of course, the experiments only simulate to some extent rather extreme situations concerning the residence of the dosage form in the gastrointestinal (G.I.) tract, e.g. a fast transition through or a long residence in the stomach. Sometimes, the dosage form does not meet highly acidic contents within the stomach. Obviously, the sequential physiological conditions to which a preparation is submitted during its passage through the alimentary canal are hardly simulated by any in vitro procedure. Information from the in vitro data may be only valuable for projection into the in vivo situation or may predict

TABLE 3

Time (h)	Bioavailability		
	Preparation A	Preparation B	Preparation C
12	88 ± 16 $0.025 < P < 0.05$	54 ± 14 $P < 0.0005$	69 ± 17 $0.0005 < P < 0.0025$
24	96 ± 16 $0.20 < P < 0.25$	69 ± 20 $0.0005 < P < 0.0025$	83 ± 21 $0.025 < P < 0.05$
32	96 ± 16 $0.20 < P < 0.25$	75 ± 24 $0.01 < P < 0.025$	87 ± 20 $0.05 < P < 0.10$

to a certain degree the performance of the dosage form in the G.I. tract, when drug delivery from the device has demonstrated to be hardly affected by changes in agitation conditions and pH of the dissolution liquids. In 'sophisticated' dissolution tests, one or more changes in the pH are included

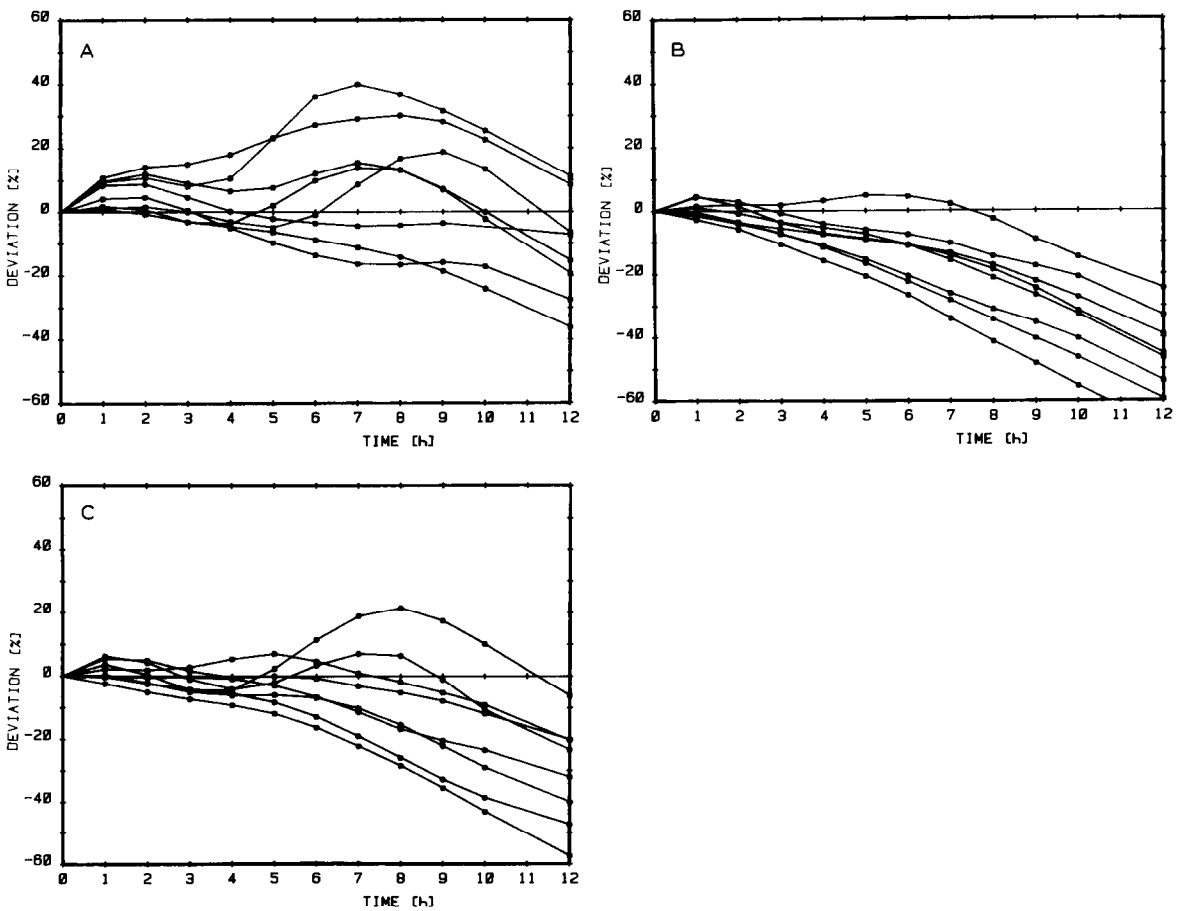

Fig. 3. A: deviation of the in vivo release plot in 8 subjects from the ideal performance—preparation A. B: deviation of the in vivo release plot in 8 subjects from the ideal performance—preparation B. C: deviation of the in vivo release plot in 8 subjects from the ideal performance—preparation C.

TABLE 4

Subject	Deviation of ideal performance (DIP)		
	Preparation A	Preparation B	Preparation C
1	0.40	0.23	0.12
2	0.12	0.14	0.16
3	0.24	0.60	0.37
4	0.18	0.32	0.13
5	0.37	0.33	0.12
6	0.09	0.45	0.22
7	0.13	0.30	0.27
8	0.24	0.50	0.44
mean ± SD	0.22 ± 0.12	0.36 ± 0.15	0.23 ± 0.12

during a dissolution run. However, these models are rather speculative about the in vivo circumstances. The pH is varied at moments and with rates, etc., that are rather arbitrary. For preparations with potential pH sensitivity of the drug release in vitro, this sensitivity may be masked, dependent on the pH change, etc., of the dissolution medium and the formulation of the preparation. The effects on the rate of drug delivery of a fast transition of the dosage form through the stomach may be poorly reflected by the results of the 'sophisticated' dissolution procedure.

As an example, the pH dependence of the drug release rate in vitro from Theolin retard could not be observed by Jonkman et al. (1981), indicating that the test suggested by them (namely the dissolution procedure described in the USP XX (apparatus 3), including a pH change after 2 h) fails as a tool in designing controlled release dosage forms.

Fig. 1A, B and C show a shaded area, determined by the confidence bounds of the in vivo theophylline release to 12 h after administration of the dosage forms. The in vitro release plots are projected in the figures; however, the 8 h of the in vitro experiment are, arbitrarily, transformed to 12 h. Fig. 1A shows, that the in vitro results of preparation A are covered by the shaded area, with the exception of the plot from the modified disintegration tester at pH 6.8. What is remarkable is the point of inflection in the in vitro as well as in the in vivo curve after about 3 and 4 h, respectively. After this point, the rate of theophylline delivery becomes rather variable. In the paddle apparatus at pH 6.8, similar variability in the release behaviour was displayed. Drug release in the modified disintegration tester at this pH was rather fast. The profile without the dip is straight and is found in the upper parts of the shaded area (Fig. 1A).

The in vitro extraction plots for preparation B (Fig. 1B) in both dissolution models in acidic conditions compare well with the area to an in vivo delivery of only about 40% of the theophylline in the devices. After a period in vivo of about 6 h, a significant decline in the rate of drug extraction in vivo is manifested, probably referring to the period of time, that the devices in a number of subjects are residing at the regions of the G.I. tract with a relatively high pH. Apparently, the impact of the pH in vivo on drug delivery from the preparation is larger than the impact suggested by the results from the in vitro tests.

Complete covering of the in vitro release plots by the shaded area was found for preparation C, except in the disintegration tester at pH 6.8. It may be concluded, that the drug delivery in vivo is in good agreement with the release from Theolin retard and preparation C in vitro in the paddle apparatus at pH 1 and pH 6.8 and in the modified disintegration tester at pH 1, only the drug released in vitro appears to be about 1.5 times faster[6].

In conclusion, the present study clearly demonstrates the adequate controlled release properties of two of the three preparations, i.e. Theolin retard and preparation C. This is for the commercial product in accordance with earlier studies.

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[6] Complete data on the in vitro and in vivo release studies are available on request.

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